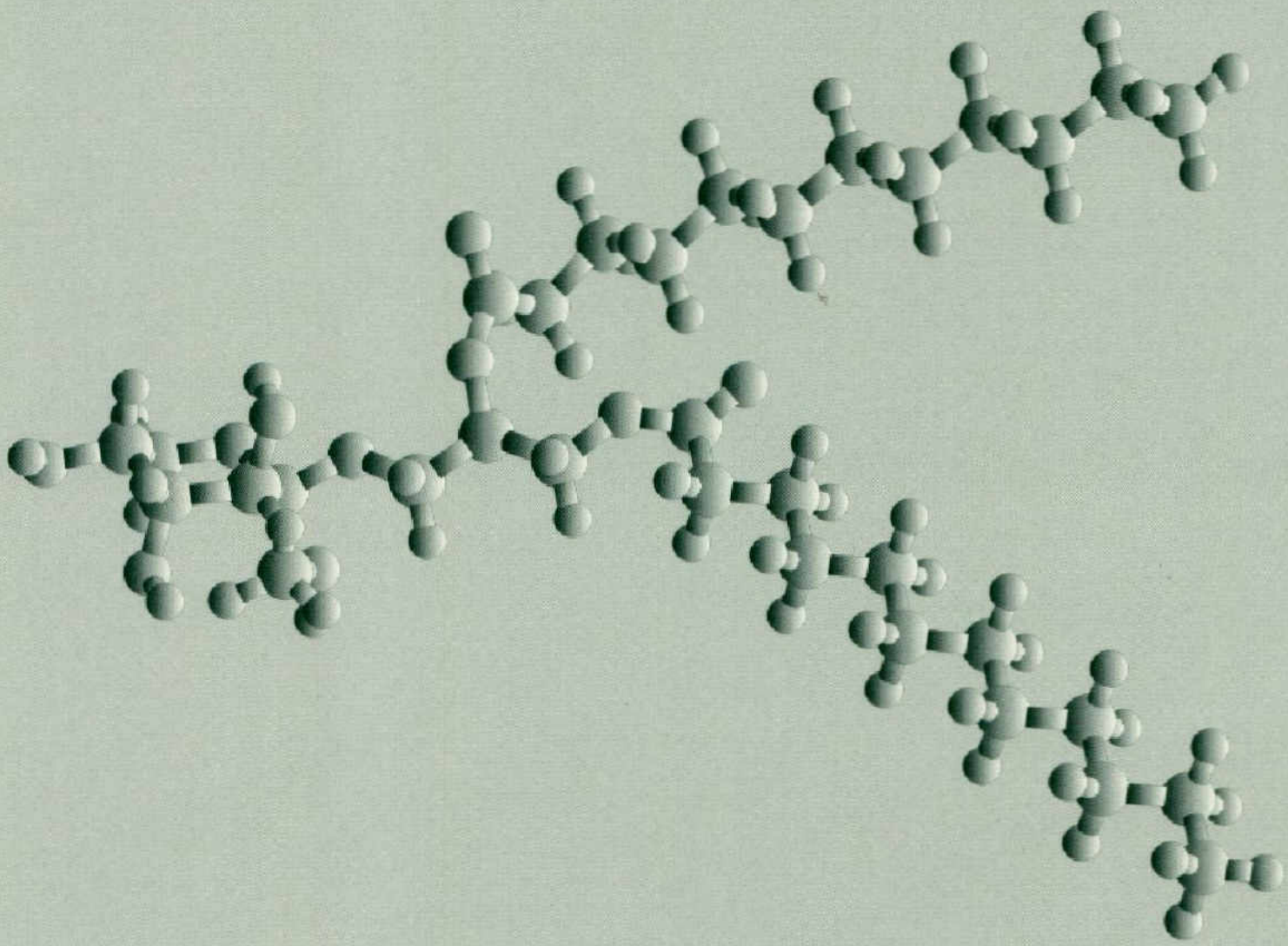
SYNTHESIS AND REACTIONS OF DIHYDROXYALKYL β-D-FRUCTOPYRANOSIDES, FRUCTOSYL LIPIDS AND RELATED COMPOUNDS



Fortunatus Sung'hwa

SYNTHESIS AND REACTIONS OF DIHYDROXYALKYL β-D-FRUCTOPYRANOSIDES, FRUCTOSYL LIPIDS AND RELATED COMPOUNDS

EEN WETENSCHAPPELIJKE PROEVE OP HET GEBIED VAN DE NATUURWETENSCHAPPEN, WISKUNDE EN INFORMATICA

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AAN DE KATHOLIEKE UNIVERSITEIT NIJMEGEN,
VOLGENS BESLUIT VAN HET COLLEGE VAN DECANEN
IN HET OPENBAAR TE VERDEDIGEN OP

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Door

FORTUNATUS SUNG'HWA

Geboren op 6 november 1963 te Kipalapala, Tanzania

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CONTENTS

CHAPTER 1

GENERAL INTRODUCTION

1.1 Carbohydrates

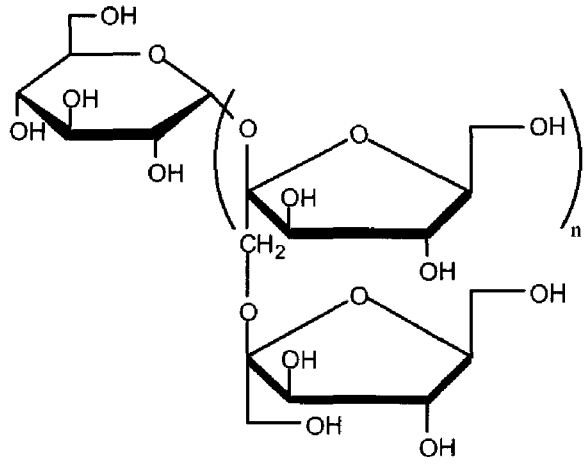
Carbohydrates are by far the most abundant class of natural organic compounds and comprise the major portion of the annually renewable biomass, currently estimated to be *ca* $2x10^{11}$ tons. They serve as a source of basic animal and human food. As energy stores of cells, they play an important role in metabolic pathways. Carbohydrates also play a vital role in other biological systems. Any malfunction of metabolism can lead to several diseases or medical disorders. These include well-known conditions such as *diabetes mellitus* and obesity.[1,2,3] Some genetic diseases are also caused by defects in sugar processing enzymes, e.g. mannosidosis and galactosemia. Cancer is often a result of defects in sugar processing enzymes that lead to uncontrolled cell proliferation. Natural carbohydrates are mainly polysaccharides, e.g. inulin (**1**), cellulose (**2**), and starch (**3**). Their traditional non-food utilization is confined to textiles, paper, and coating industries either as such, or in the form of simple esters or ethers.

Inulin (a 1,2-β-D-polyfructofuranoside) (**1**) is commonly found as a reserve carbohydrate in tuberous plants such as Jerusalem artichoke (*Helianthus tuberosum*) and chicory (*Cichorium intybus*). The production of sisal fibre in Tanzania from the leaves of *Agave sisalana* represents 26% of the country's agricultural exports, and 19% of the total African production. It is characterized by the simultaneous production of large amounts of waste materials which also contains inulin. During the production of the fibres, only 5% of the leaves are used and the remaining 95% is waste. Sisal waste is amongst the most troublesome in Tanzania. It is estimated that approximately 234,000 tons are produced per annum during this process. This is either left to rot or is discharged into water systems. Other methods which are used for the disposal of these wastes include "slash and burn" operations. All of these methods cause pollution of the environment. Inulin in the sisal stems serves as a reserve carbohydrate and as an osmolyte to extract water from the soil. With a potential inulin source of up to 30% (w/w) from the waste material, the production of inulin could be focused on these wastes, not only for commercial purposes but also as a means of reducing environmental pollution.

The bulk of the enormous quantity of the various natural carbohydrates decays and is recycled by natural processes. Only ~ 3% of it is used by man despite considerable efforts to increase the use of this inexpensive bulk-scale raw material. This is probably due to two main factors (i) the use of fossil-based material is currently more economical and (ii) the technology to convert petrochemical raw material into a broad range of products is better developed.

There is presently a growing interest from industry to develop the use of simple carbohydrates as a source of chemical raw materials. This is due to the fact that carbohydrates are annually renewable products in contrast to petrochemicals, which are derived from non-

regenerable fossil feedstocks. In addition, carbohydrates and their derivatives are relatively cheap and most of their products are readily bio-degradable and non-toxic, which makes them relatively harmless to the environment. Products of interest derived from carbohydrates include compounds with amphiphilic properties (*vide infra*) some of which have been found also to possess interesting biological activities, e.g. anti-tumour,[4a-e] bactericidal[5] and plant growth inhibition.[6] Others, depending on the solubility characteristics and physical properties, are used in the manufacture of detergents, emulsifiers, dispersing or wetting agents.



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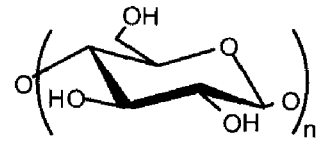
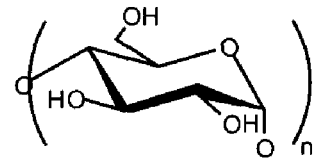


2

n >1000



3

n >200

1.2 Carbohydrates-based amphiphiles

Carbohydrate amphiphiles are molecules which contain a hydrophobic and a hydrophilic moiety. The hydrophobic section consists usually of one or two long-chain aliphatic (saturated, unsaturated, linear or branched) units and this is linked to a hydrophilic carbohydrate fragment. These molecules have surface activity as a consequence of their molecular structures. In aqueous solutions they tend to form micelles, vesicles, bi-layers and other aggregates. A condition is achieved so that the hydrophobic areas are withdrawn from the surrounding water, and the hydrophilic head groups are directed towards the aqueous phase. Aggregate formation occurs only above a certain limiting concentration. This is known as the critical micelle concentration (CMC) which is a characteristic for each surfactant. Oriented monolayers are formed at phase borders which results in a decrease of the surface tension between water and the adjacent phase. The surface tension decreases with increasing concentration of the amphiphile until the CMC value is attained. The temperature of the system is also important since aggregate formation occurs only above a certain value, the Krafft point.

Various carbohydrate-based amphiphiles also have liquid crystal properties. Various aspects of their behaviour in this respect and the required structural elements have been reviewed.[7] There is a considerable variation of type now available with appropriate synthetic procedures. Most of these have concentrated on the use of cheap and friendly reagents in short reaction sequences. The most interesting current, commercially available, sugar surfactants are

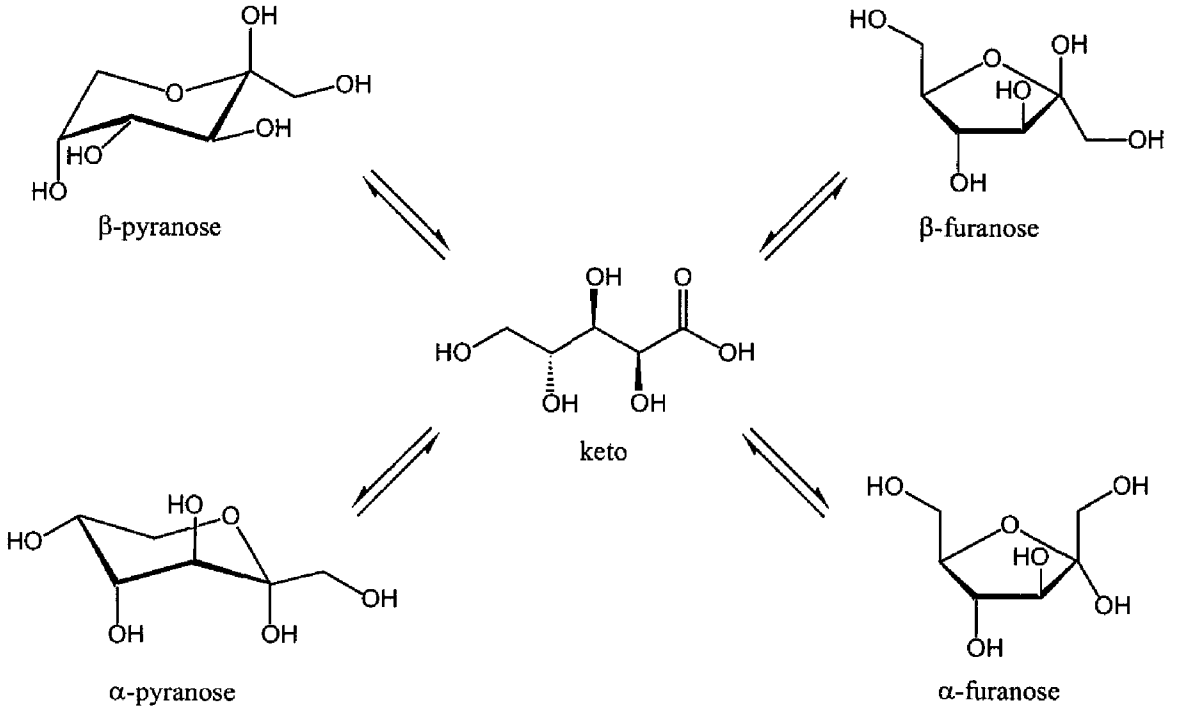
long-chain esters of sucrose and alkyl(poly)glucosides. They are applied as emulsifiers in food, cosmetics and pharmaceuticals. In this respect glycolipids, especially the glycerol glycolipids (*vide infra*) must be considered as the most natural, fundamental and original carbohydrate-based amphiphiles.

There is a need to develop the chemistry of D-fructose (*vide infra*) much further than its present status. The systematic elaboration of some of its more easily available reaction products is required. Its current cheap bulk price, *ca.* 1.00 US dollar per kg and its ready availability from inulin-producing crops makes it a particularly attractive basic material for producing materials such as carbohydrate-based amphiphiles. The current situation of the sisal industry in Tanzania, which produces a considerable amount of by-products containing inulin, would give an extra impetus to this aim (see section 1.1).

1.3 D-Fructose

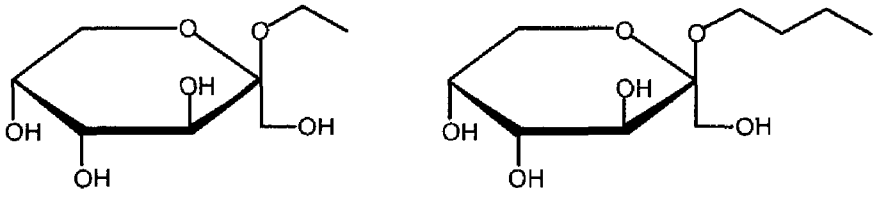
D-Fructose is the second most abundant naturally occurring monosaccharide. It occurs generally in the β-furanosyl form in sucrose or in plant and bacterial polysaccharides.[8] These compounds possess interesting bio-functional properties and are involved, for example, in defence mechanisms against micro-organisms or as food reservoirs.[9a] As a consequence of their biological importance, various enzymatic and chemical methods have been studied for the synthesis of D-fructofuranosyl derivatives.

The chemistry of D-fructose has not developed at the same rate as that of D-glucose with respect to most known derivatives.[9b] This is due to the fact that D-fructose, unlike the aldoses and other ketohexoses exhibits complex mutarotational behaviour in many of the solvents commonly used in reactions, these include *N,N*-dimethylformamide, dimethyl sulfoxide, pyridine and water. The ratio of the five possible tautomers (scheme 1.1) depends on the solvent, time, temperature, and concentration. The effects of these variables have been studied using ^{1}H-NMR spectroscopy.[10] This observation makes it difficult to specify precise reaction conditions, e.g. acylation in pyridine, that are consistently repeatable. Chromatography is usually required to separate the products of these reactions, which is cumbersome, time consuming and usually signifies poor yields. This is manifestly so with glycosidation reactions. The synthesis of specifically defined crystalline fructosides is rather difficult. Normal acid catalysed glycosidation is temperamental and tends to lead to complex mixtures of furanosides and pyranosides, together with dehydration-degradation products depending on the reaction conditions. Fructopyranosides and fructofuranosides, unlike aldosides,[11] are hydrolysed at similar rates, so that overall control of ring size during these reactions is difficult to achieve. Alternative routes based on Koenigs-Knorr-type procedures are also difficult because of a scarcity of suitably protected, activated intermediates, together with complications arising from competitive ortho ester formation.[12]



Scheme 1.1: Tautomeric forms of **D**-fructose in solution

In view of **D**-fructose being the second most abundant naturally occurring monosaccharide, it is also surprising that there are not more natural products containing **D**-fructose linked glycosidically to a variety of alternative aglycons. Its main occurrence seems restricted to a widely distributed, but limited group of di- and oligosaccharides, in which it is present in the furanose form. This group includes sucrose, raffinose, inulin, and various other levans. There are few examples of **D**-fructose occurring naturally in the pyranose form despite it being that of the pure crystalline compound. Some simple alkyl pyranosyl derivatives have been claimed to have medicinal properties. Ethyl β-**D**-fructopyranoside (**4**) has been isolated [13] from the pericarps of *Rosa davurica* (Rosaceae) and the butyl derivative **5** from *Liriope spicata* prolifera roots, [14] both plants are used in traditional chinese medicine. Some simple synthetic alkyl β-**D**-fructopyranosides have been claimed to suppress Ig-E antibody formation.[15]



4 **5**

It is even more surprising that no lipid structures containing a fructose unit have been reported so far. Glycolipids are very widely spread in nature and simple glycosylated glycerol derivatives are ubiquitous in the majority of life forms, especially plants (see section 1.5). The possible formation of glycerol fructosides during the enzymatic synthesis of some levans from sucrose has been implied but not substantiated.[16] The reaction of **D**-fructose with glycerol in the presence of mesoporous materials (e.g. MCM-41) as catalyst has been reported recently.[17] A

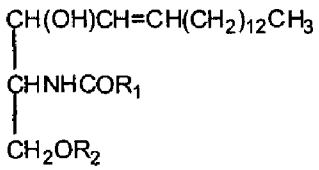
complex mixture of at least six different products was formed (GC analysis) but was not investigated further. Gonzalez *et al.*[18] have recently reported the enzymatic synthesis of some fructosyl glycerol derivatives from sucrose using levan sucrases obtained from *B.subtilis* and *B.circulans*. Various aspects of the reaction were investigated and it was shown that there was only a slight preference for substitution at C-1 / C-3 over that at C-2 (see Chapter 2 for detailed discussion). There is a need to investigate further the formation of fructosyl glycolipids and derivatives thereof, which could have interesting biological and amphiphilic properties (see section 1.2).

1.4 Simple classification of glycolipids

Glycolipids are commonly found in all living organisms. Structurally, they comprise a carbohydrate moiety, as a mono or oligosaccharide, which is linked to the "lipid" portion through the glycosidic centre. The two most common types of glycolipids are based on sphingosine and glycerol, but other types are also known.

(i) *Sphingosine*-type

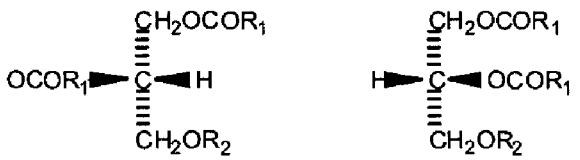
These are derivatives of long chain aliphatic 2-amino-1,3-diols of which **D**-erythro-1,3-dihydroxy-2-amino-4,5-*trans*-octadecene is the base most commonly encountered. Fatty acids saturated, unsaturated or hydroxylated are linked by an amide bond at C-2 of the sphingosine unit and a sugar moiety is linked glycosidically to the hydroxyl function at C-1.



R_1= long-chain alkyl ester or ether group
R_2= sugar group

(ii) *Glycerol*-type (glyceroglycolipids)

These are derivatives of glycerol in which a carbohydrate portion is linked glycosidically to the C-1 / C-3 position of a glycerol moiety, with fatty acids residues being linked to the remaining hydroxyl groups of the unit as esters. Some structures have long-chain alkyl ether groups linked to these positions instead of ester groups.



R_1= long-chain alkyl ester or ethergroup
R_2= sugar group

(iii) Ester type

These are esters of carbohydrate derivatives where complex fatty acids are attached to positions other than the C-1 (glycosidic) of the carbohydrate portion, e.g. alkyl glycosides with a long chain ester group attached to the C-6 position.

(iv) Steryl glycosides

An oligosaccharide or an acyl derivative of an oligosaccharide is linked glycosidically to a hydroxyl group of a sterol unit.

In the following sections only glycolipids of the glycerol-type will be discussed in detail since they form the basis of this thesis.

1.5 Glycosyl glycerol derivatives

Glycosyl glycerols and their derivatives are widely distributed in nature, they are found in all higher plants, animal tissue, algae, marine organisms and in bacteria. They usually occur esterified either with saturated or unsaturated fatty acids on their glycerol sub-units. In other types these esters groups are replaced by long-chain ether groups. Structurally, these naturally occurring carbohydrates can exhibit a large variety, since their structures can differ with the nature of the glycosyl unit (a monosaccharide- usually **D**-glucopyranose or **D**-galactopyranose or an oligosaccharide), the position and the anomeric configuration of the linkage of the sugar to the glycerol unit, and the nature of the fatty acyl moieties. Glycosyl diglycerides are also common components of the lipids of many gram-positive bacteria. Earlier studies showed that such compounds were present in *Micrococcus lysodeikticus*.[19] Further studies reported the occurrence of these compounds in species of *Pseudomonas* [20] and *Pneumonococcus*,[21] and *Streptococcus faecalis*.[22] These indicated [23a-d] that glycosyl diglycerides containing galactose, glucose, or mannose appear to be almost as ubiquitous in gram-positive bacteria as galactosyl diglycerides are in photosynthetic micro-organisms and plants.

1.6 Galactosyl lipids

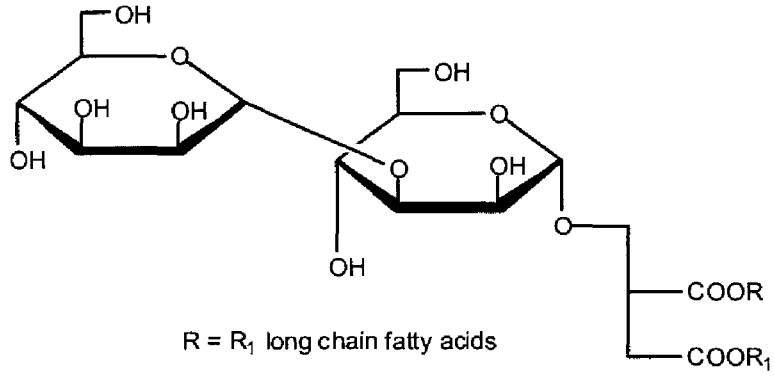
These are the most common type of the simple naturally occurring derivatives and have been isolated from a variety of sources. Colin *et al.* reported that galactosyl glycerols also occur in many red algae.[24,25] Putman and Hassid [26] observed that marine alga *Irideae laminarioides* contain floridosides (1-4%). These galactolipids are also widely distributed throughout the plant kingdom,[27,28] especially in the photosynthetic tissues.[29,30] They also occur in small amounts in other parts of plants,[31,32] e.g. bulbs, flowers, fruits and roots. At the sub-cellular level, these glyceroglycolipids are mainly located in the chloroplast fractions of the leaves.[33,34]

The presence of α-**D**-galactosylglycerides has been shown in avocado fruits [35] and potato tubers.[36] Carter *et al.*[37,38] isolated two main **D**-galactosylglycerides, mono-*O*-**D**-galactosyl-glycerides (MGDG) and di-*O*-**D**-galactosylglycerides (DGDG) from wheat flour. These glyceroglycolipids have also been found to possess pharmacological activity. Mono-*O*-**D**-galactosylglycerides (MGDG) and di-*O*-**D**-galactosylglycerides (DGDG) inhibit tumour promotion *in vitro*, and the strength of the activity was found to depend on their acyl substituents.[39]

Higher homologs of di-*O*-**D**-galactosylglycerides (DGDG), 1-*O*-(tri- and tetra *O*-**D**-galactosylglycerides) have also been detected in some plant tissues.[40]

1.7 D-mannosyl-*O*-D-mannosyl-di-acylglycerols

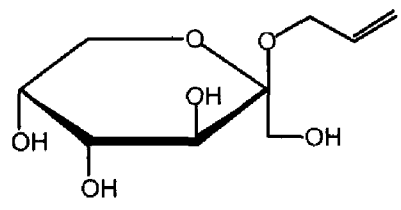
These types of glycolipids have been found to occur mostly in micro-organisms, such as *Micrococcus lysodeikticus, Microbacterium lacticum* and *Arthrobacter globiformis*. In most cases the fatty acid content found associated with this glycolipid comprises 70 to 80% of 12- and 13-methyltetradecanoic acids.[41]



α-D-Mannopyranosyl α-D-mannopyranosyl diglyceride

1.8 Aim of the study

The capriciousness of glycoside formation from **D**-fructose was discussed earlier (see section 1.3). Currently, there are still less than 30 known, simple, well-defined, crystalline fructosides of either ring size. This does not include natural saccharides, such as sucrose, raffinose, etc. One of these is allyl β-**D**-fructopyranoside (**6**) which is easily obtained [42] by treatment of **D**-fructose with allyl alcohol in the presence of a catalytic quantity of anhydrous hydrogen chloride. It is the aim of this study to investigate the asymmetric dihydroxylation of derivatives of the glycoside **6** as a route to **D**-fructopyranosyl-*sn*-glycerols, and some long-chain fatty acid esters thereof. The conversion of the products into a number of sterically-defined, active derivatives including oxiranes, aziridines, and thiiranes will also be described. The studies were also intended to improve the overall knowledge of the chemistry of **D**-fructose.



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1.9 Outline of the thesis

Chapter 1 gives a general introduction to carbohydrates, glycosidic glycerols and other related compounds. Their occurrence and the distribution of these compounds in nature, and the general role played by these naturally occurring products to support life in living organisms are described briefly. Some potential applications of these compounds are also presented.

Chapter 2 provides a brief literature review of simple glycolipids (glycosyl glycerols) and other related compounds with special references to the various synthetic approaches that have been used to synthesize these compounds.

Chapter 3 describes the synthesis of some 2(*R*),3-dihydroxylpropyl β-**D**-fructopyranoside (1-*O*-β-**D**-fructopyranosyl-*sn*-glycerol) derivatives by the asymmetric dihydroxylation of the double bond in protected derivatives of allyl β-**D**-fructopyranoside.

Chapter 4 deals with the synthesis and reactions of some spiro-fructosides and *quasi*-disaccharides derived from **D**-fructopyranosyl glycerol derivatives, and the reductive ozonolysis of allyl β-**D**-fructopyranoside.

In Chapter 5 the synthesis of some acylamino derivatives from (*2R*),3-dihydroxyl-propyl β-**D**-fructopyranoside (1-*O*-β-**D**-fructopyranosyl-*sn*-glycerol), is reported.

Chapter 6 describes the synthesis of some amido-phosphate derivatives as potential surfactants from β-**D**-fructopyranosyl glycerol and related compounds.

In Chapter 7 the synthesis and some oxidation reactions of but-2-enyl β-**D**-fructopyranoside, obtained by Fischer-type glycosidation of **D**-fructose with crotyl alcohol, are presented.

Chapter 8 describes the synthesis of some thiiranes derived from 2(*R*),3-dihydroxylpropyl β-**D**-fructopyranoside and related derivatives.

Chapter 9 reports on the synthesis of a glyceryl-ether and some related compounds from 2,3:4,5-di-*O*-isopropylidene β-**D**-fructopyranose.

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CHAPTER 2

GLYCOSYL GLYCEROLS AND RELATED GLYCOLIPIDS: A BRIEF LITERATURE REVIEW OF SYNTHESIS

2.1 Introduction

Glycosides of glycerol are important basic units of glyceroglycolipids. These are widely distributed in nature and have been isolated from many sources including plants, animal tissue, bacteria and marine organisms.[1a-c] The glycerol sub-units are usually esterified, or etherified, with a wide variety of long chain fatty acid or ether residues. There has been a recent resurgence of interest in these compounds because of newly discovered biological properties, including *inter alia*, anti-tumour and anti-inflammatory promoting activities.[2a-c] Besides the above mentioned biological properties, these compounds have also been found to possess other functions in nature, such as in the biosynthesis of fatty acids [3-5] and electron transport in plants.[6]

Unsubstituted glycosidic glycerols are highly water soluble materials, having a neutral net electric charge, and show no toxicity towards enzymes when assayed *in vitro* at high, but physiological, concentration. These features make them useful as osmolytes in nature. In addition, they are also of particular interest since they are suitable as moisturizers in cosmetics due to their friendly behaviour towards skin.[7,8] The outermost skin layer, termed horn skin, is protected against "drying out" by water binding substances which are known as "natural moisturizing factors" (NMF), e.g. carbohydrates, amino acids, urea, etc. These substances (NMF) dissolve in water during washing and result in roughened and chapped skin. Moisturizing creams need to contain substances of the NMF group, or have similar moisture-regulating components.

Glycosyl glycerols are also important as glycoconjugates, especially in their diacylglyceryl ester forms. These compounds exhibit surfactant character having a carbohydrate moiety as a polar head group, and a non-polar fatty ester group with hydrophobic behaviour. Depending on their structure and nature of the solvent, these surfactants are able to form micelles, monolayers, double layers, vesicles (liposomes), liquid crystalline phases and other associated properties. Glycosyl diglycerides also show the ability to encapsulate other substances in solution, this property makes these compounds interesting as bio-degradable surfactants in shampoos and soaps, and also as transporters of cosmetic or medicinal components.

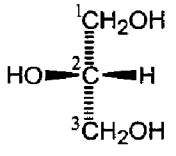
Currently, there is interest in synthetic routes with the aim of supplying large, and pure, quantities of such materials so that their physico-chemical properties and potential applications can be further studied. The synthesis of glyceroglycolipids can be carried out using various approaches. These include, coupling of a suitable glycosyl donor with (i) a chiral glycerol derivative, often derived from D-mannitol, or (ii) a racemic glycerol derivative, followed by the

separation of the diastereoisomeric 1-*O*- and 3-*O*-glycosylated product. Route (i) has been more thoroughly explored [9,10a-f] compared to route (ii) which could profitably shorten the number of synthetic steps. Some progress in obtaining these compounds by employing enzymatic approaches has been achieved recently, *via* transesterification mediated by lipases in the presence of different organic solvents and acyl donors.[11] More recently, the syntheses of fructosyl glycerols have been accomplished by levansucrase from *Bacillus circulans* / *Bacillus subtilis*, using sucrose as the fructosyl donor in the presence of glycerol.[12]

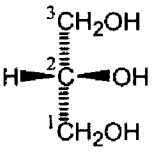
Some aspects of the syntheses of these compounds using various approaches are described briefly in this chapter which are pertinent to the contents of this thesis. They illustrate that many of the procedures commonly used could not be applied to obtain derivatives of **D**-fructose because of its inherent difficult chemical nature.

Nomenclature of glycoglycerolipids [13]

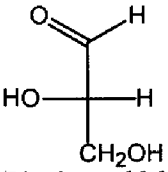
Some esters and ethers of glycosyl derivatives of glycerol are chiral, and are designated by a prefix (*sn*), denoting the substituent, preceded by a locant. A numbering system is used to indicate that the primary alcohol groups are not interchangeable, the carbon atoms of glycerol are numbered stereospecifically. If the secondary hydroxyl is shown to the left of C-2 in a Fischer projection, the carbon atom above C-2 is called C-1, the one below C-3. To differentiate this numbering system from others that have been used, the glycerol is always accompanied by the prefix '*sn*' (for stereospecifically numbered). The prefix '*rac*' (for racemic) is used when the product is a racemic mixture of both diastereoisomers. Since glycerol is a derivative of glyceraldehyde, the two stereochemical descriptors, **D** and **L** were used previously to define the position of the hydroxyl group at C-2. If the hydroxyl group attached to C-2 is to the left, the **L**-configuration was used, and when the hydroxyl group attached to C-2 is pointing to the right, the **D**-configuration was used. Some examples are given below. A considerable amount of confusion prevails in the literature on the presentation of the correct stereo structures using this system (cf. p. 7 ref. 43).



glycerol (*sn*-numbering)

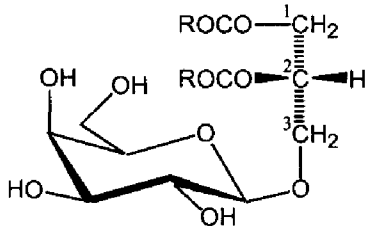


glycerol (*sn*-numbering)

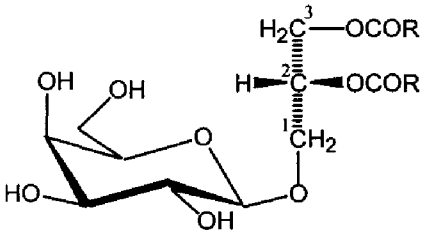


(L)-glyceraldehyde

Examples



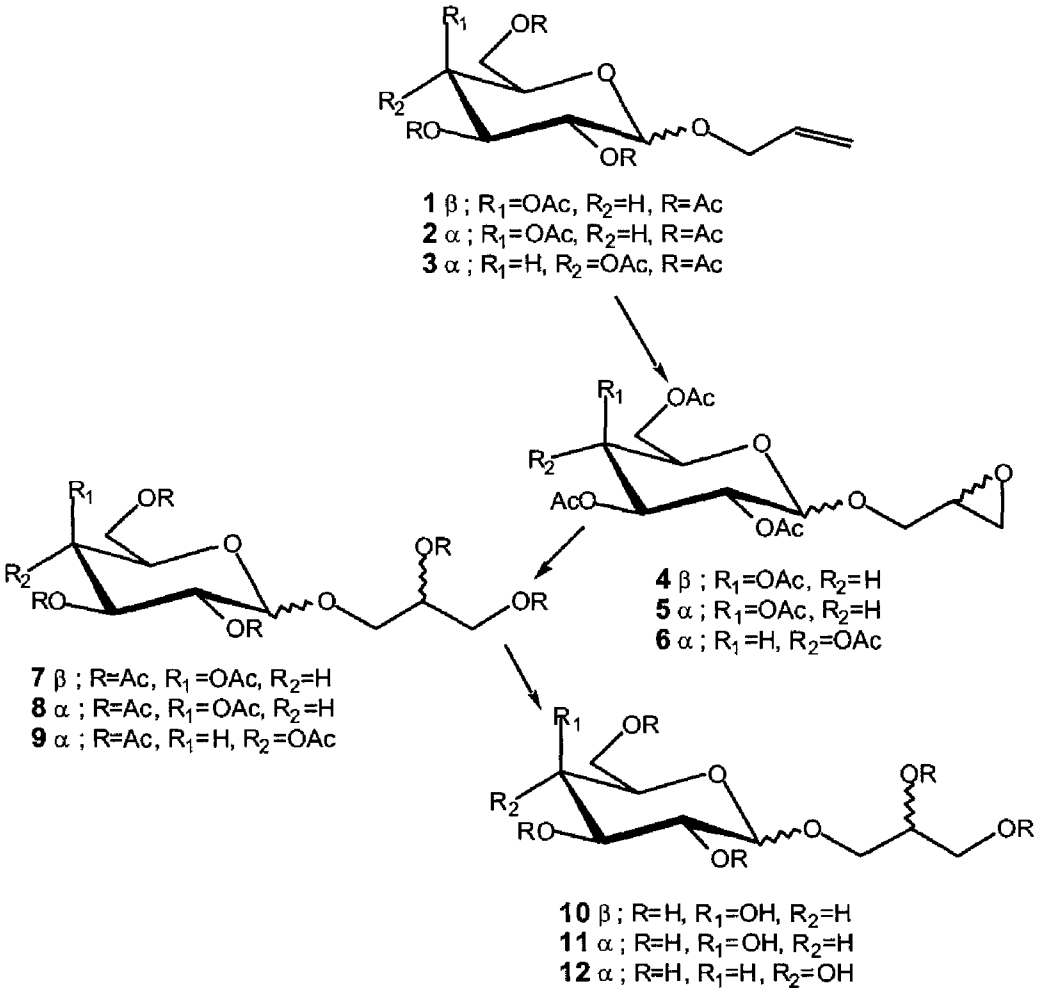
1,2-di-*O*-acyl-3-*O*-β-**D**-galactosyl-*sn*-glycerol



2,3-di-*O*-acyl-1-*O*-β-**D**-galactosyl-*sn*-glycerol

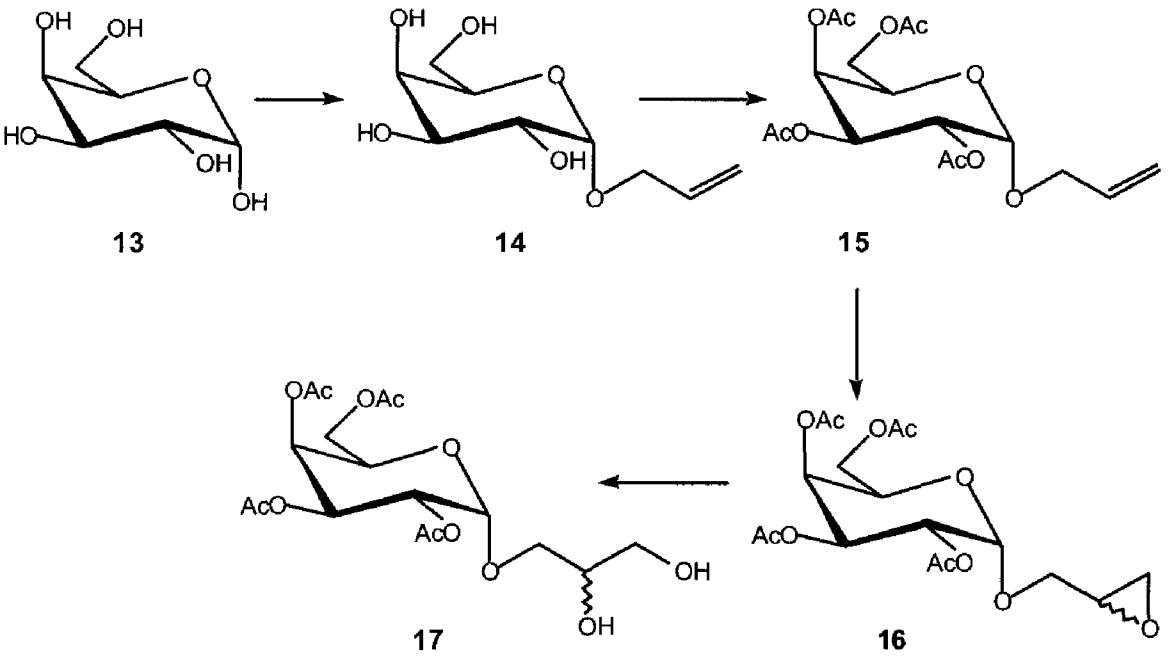
2.2 Synthesis of 1-*O*-(glycopyranosyl)-*rac*-glycerols

Allyl glycosides are important intermediates in carbohydrate chemistry for temporary protection of the anomeric centre.[14-16] They are also useful as monomers for the synthesis of glycopolymers.[17] Suhr *et al* [18] reported the conversion of the allyl tetra-*O*-acetyl-glycosides **1**, **2** and **3** into glycosyl glycerols [19] using a three step procedure (Scheme 2.1). The β-**D**-galactoside **1** was easily prepared from β-**D**-galactose peracetate by reaction with allyl alcohol in the presence of boron trifluoride-etherate as a catalyst.[20] The α-linked compounds **2** and **3** were synthesized using a straightforward Fischer glycosidation reaction, [21] but considerable amounts of the β-**D**-products were also produced.[22,23] The compounds **1**, **2**, and **3** were reacted in the usual manner with *m*-chloroperbenzoic acid in dichloromethane to give the oxiranes **4**, **5**, and **6**, but with little diastereoselectivity (1:0.82; 1:0.72; 1:0.82). Reaction of the 2,3 epoxypropyl glycosides with acetic anhydride in the presence of boron trifluoride-etherate as the catalyst yielded 1,3-di-*O*-acetyl-(2',3',4',6'-tetra-*O*-acetyl-glycopyranosyl)-*rac*-glycerols (**7**), (**8**) and (**9**). Deprotection of these compounds to give the 1-*O*-(glycopyranosyl)-*rac*-glycerols (**10**), (**11**) and (**12**) was carried out under the usual conditions, i.e. a Zemplen trans-esterification with sodium methoxide in methanol.



Scheme 2.1: Synthesis of 1-*O*-(glycopyranosyl)-*rac*-glycerols **10,11** and **12**

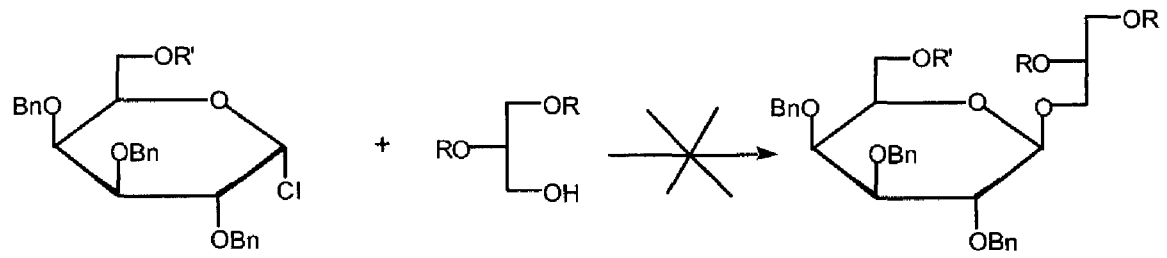
A similar synthetic approach was also employed for the synthesis of racemic 2,3-dihydroxypropyl-α-D-galactopyranoside (**17**) (isofloridoside). The allyl glycoside **14** was obtained from α-D-galactose **13** by treatment with allyl alcohol saturated with hydrogen chloride gas.[24] The product was acetylated to yield **15**, which was converted to the oxirane **16** by reaction with *m*-chloroperbenzoic acid in dichloromethane. Treatment of **16** with methanolic sodium methoxide, and thereafter, with perchloric acid afforded isofloridoside **17**.[25] A shortcoming was that the reaction was performed on a very small scale and the product was not characterized.



Scheme 2.2: Synthesis of 2,3-dihydroxypropyl α-D-galactopyranoside (**17**)

2.3 Synthesis of 3-*O*-β-D-glycosyl glycerols

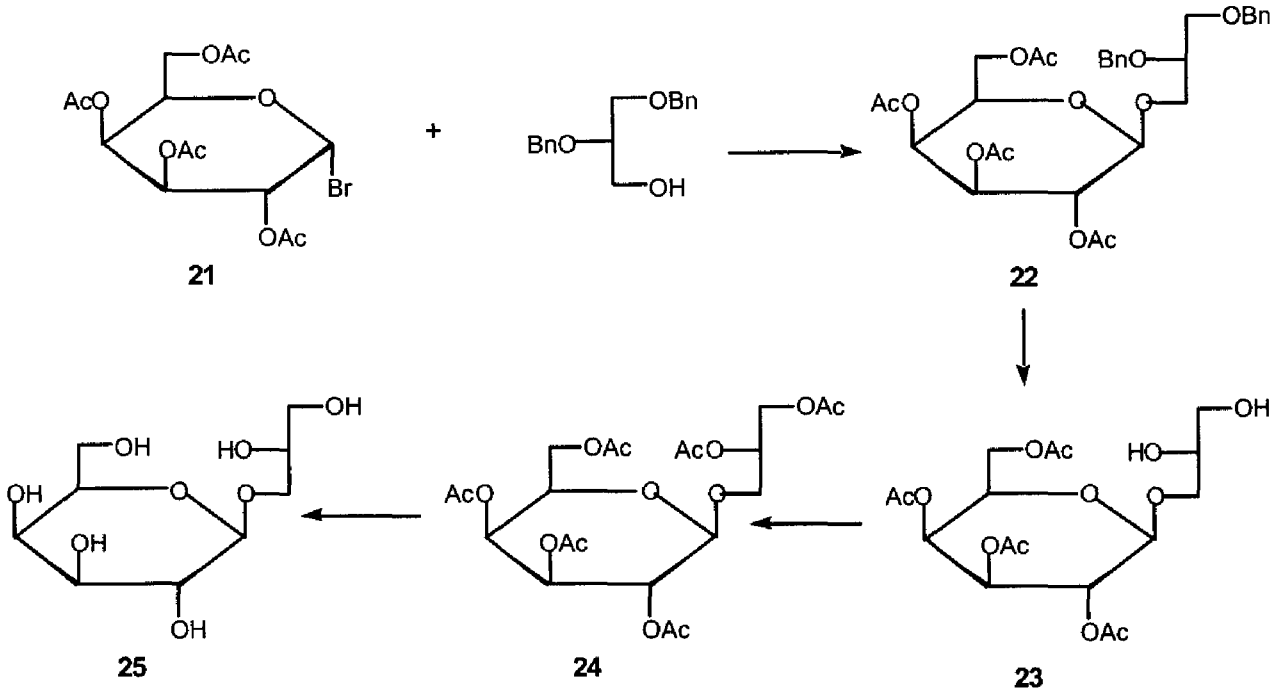
Several attempts have been made to synthesize 3-*O*-β-D-glycosyl-*sn*-glycerols involving the condensation of 1,2-bis-*O*-(2-methylallyl)-L-glycerol (**19**) with a glycosyl chloride. The reaction conditions were the same as those that Kronzer and Schuerch[26] showed to be suitable for the preparation of β-methyl glycosides from glycosyl chlorides containing a non-participating group at the C-2 position. Condensation of the chloride **18** with compound **19** using these conditions [26] was not successful. Stevens *et al.*[27] reported that glycosyl chlorides containing non-participating groups at the C-2-position react readily with a large excess of methanol in the presence of silver carbonate or mercury (II) cyanide to give methyl β-glycosides stereospecifically. When 2,3,4,6-tetra-*O*-benzyl α-D-glucopyranosyl chloride (**18**) was treated with 1,2-bis-*O*-(2-methylallyl)-L-glycerol (**19**) under these conditions, none of the expected product **20** [28] was obtained.



R'= CH_2-CH=$CHCH_3$
R = CH_2-$C(CH_3)$=CH_2

The interaction of the alcohol **19** with silver carbonate was then studied in some detail, [29] and from the results it was be postulated that the unsaturated centre of the 2-methylallyl groups in compound **19** interacted with silver ions to prevent the hydroxyl group presenting itself in the correct orientation required for glycoside formation, by a mechanism described earlier.[30]

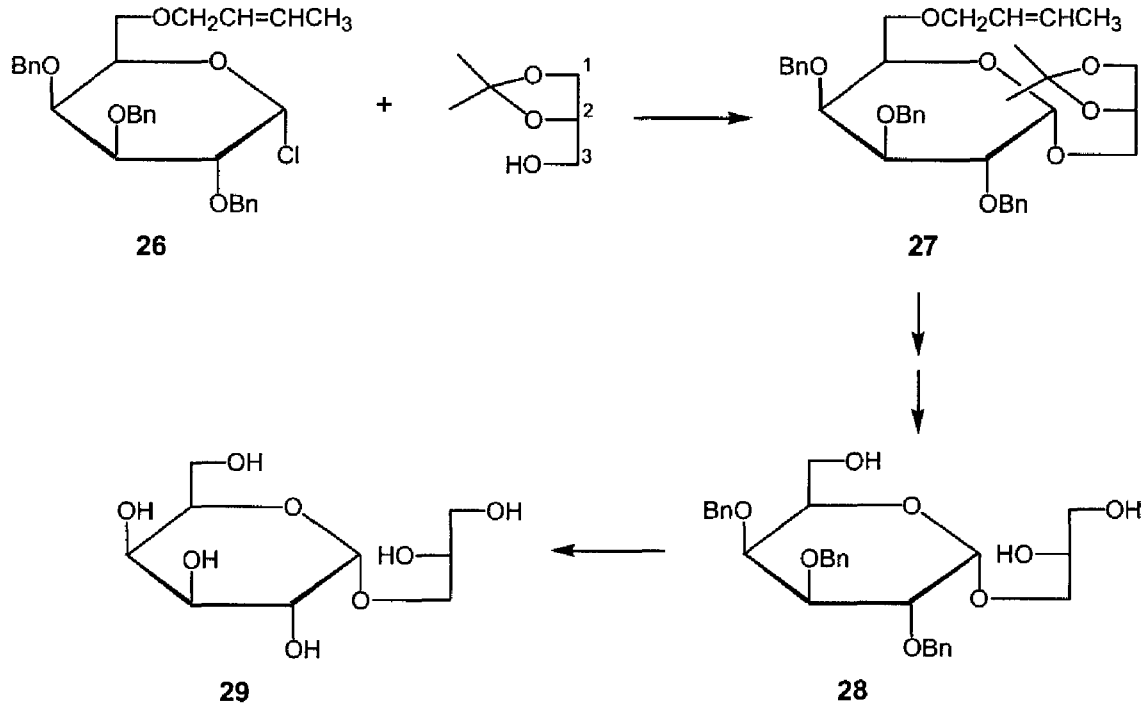
The condensation reaction of tetra-*O*-acetyl α-**D**-galactopyranosyl bromide **21** with 1,2-di-*O*-benzyl-*sn*-glycerol in the presence of mercury(II) cyanide in benzene / nitromethane (1:1) [31] yielded the glycoside **22** as the main product. Removal of the benzyl groups by hydrogenolysis and subsequent treatment of the product **23** with acetic anhydride / pyridine in the usual manner afforded the hexa-acetate **24** which could be hydrolyzed to give 3-*O*-(β-**D**-galactopyranosyl)-*sn*-glycerol **25** [28] (Scheme 2.3).



Scheme 2.3: Synthesis of 3-*O*-(β-**D**-galactopyranosyl)-*sn*-glycerol (**25**)

Attempts have also been made to synthesize the α-anomer of compound **25**. Compound **26** was condensed with 1,2-*O*-isopropylidene-**L**-glycerol under conditions described for the synthesis of the 1,2-*cis*-glycoside [32] (Scheme 2.4). The glycoside **27** that was obtained was then

treated with potassium *t*-butoxide in dimethyl sulfoxide [33] to remove the but-2-enyl group, and then with dilute aqueous acid to remove the isopropylidene group to give 3-*O*-(2',3',4'-tri-*O*-benzyl α-**D**-galactopyranosyl)-**L**-glycerol (**28**), which was obtained as a syrup. The product was subjected to hydrogenolysis to remove the benzyl groups and the product obtained was crystallised from ethanol / methanol to give the known[34] 3-*O*-(α-**D**-galactopyranosyl)-**L**-glycerol (**29**) in 46% yield.[28] It has been found that although this reaction is usually stereoselective for α-glycoside formation, there is also a possibility of the β-**D**-glycoside being obtained as a by-product in small amounts (*ca* 10%).[32]



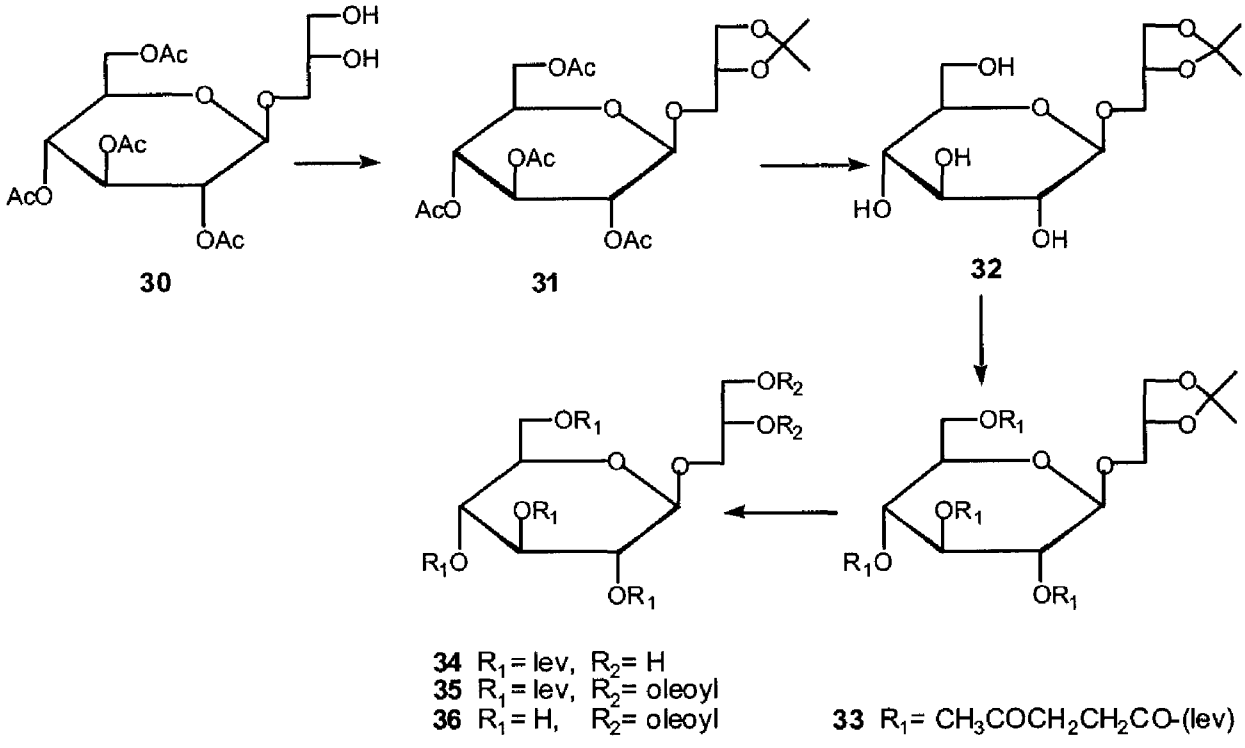
Scheme 2.4: Synthesis of 3-*O*-(α-**D**-galactopyranosyl)-**L**-glycerol (**29**)

2.4 Synthesis of mono- and diester derivatives of glycosyl glycerols

Glyceroglycolipids usually occur with the hydroxyl groups of the glycerol moiety esterified with a variety of saturated or unsaturated long chain fatty acids. The biological function, as well as occurrence and distribution of these products, has been an area of intense interest and investigation.[35a-f] Some of these compounds have pharmacological activity, e.g. digalactosyl diacylglycerols (DGDG) possess anti-tumour promoting activity, [36] monogalactosyl diacylglycerols (MGDG) can act as anti-inflammatory substances [37] and sulfoquinovosyl diacylglycerols are active against the human immunodeficiency virus (HIV).[38]

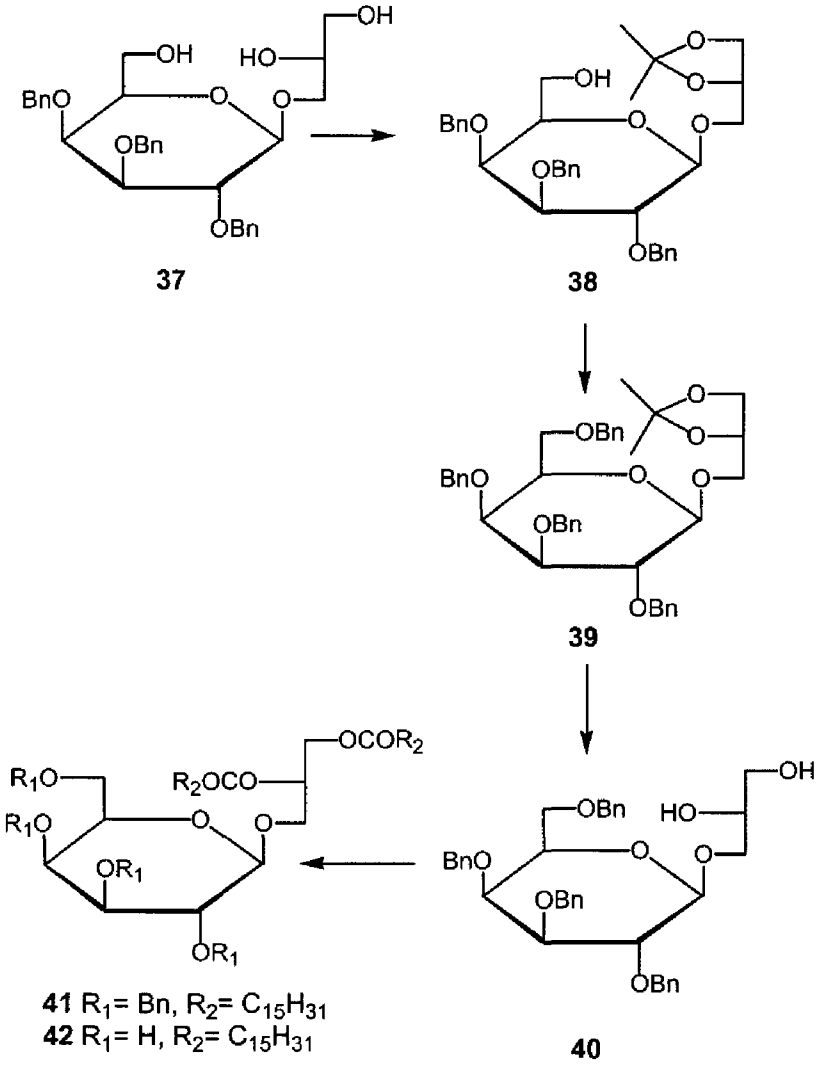
The synthesis of these compounds usually involves the acylation of hydroxyl groups of protected glycosyl glycerol using fatty acid chlorides as acylating agents. The synthesis of 3-*O*-(β-**D**-glucopyranosyl)-1,2-di-*O*-oleoyl-*sn*-glycerol (**36**) from the acetylated β-**D**-glucosyl glycerol derivative **30** involved four steps (Scheme 2.5). In the first step, the two hydroxyl groups of the glycerol moiety of **30** were simultaneously protected by reaction with 2,2-dimethoxypropane in the presence of a catalytic amount of *p*-toluenesulfonic acid to give

crystalline 3-*O*-(2',3',4',6'-tetra-*O*-acetyl β-**D**-glucopyranosyl)-1,2-*O*-isopropylidene-*sn*-glycerol (**31**). The base labile acetyl groups of **31** were then removed using a catalytic amount of sodium methoxide in dry methanol to afford **32** in quantitative yield. The third step involved the selective protection of the glucose unit with levulinoyl groups.[39] The levulinoyl protecting function, which has been also used successfully in nucleotide synthesis [39,40] and carbohydrate chemistry, [41,42] can easily be removed under neutral condition without causing the hydrolysis of other esters groups. Thus, reaction of **32** with levulinic (4-oxopentanoic) acid anhydride, in the presence of 4-dimethylaminopyridine (DMAP) as the catalyst, gave **33**. Treatment of **33** with aqueous acetic acid gave 3-*O*-(2',3',4',6'-tetra-*O*-levulinoyl β-**D**-glucopynanosyl)-*sn*-glycerol (**34**) [43] which was then acylated with oleoyl chloride [44] to yield **35**. Removal of the levulinoyl protecting groups by treatment with hydrazine hydrate in a pyridine-acetic acid mixture gave compound **36**, which was purified by column chromatography. (N.b.: The authors [43] have inadvertently presented the glycerol moiety as the alternative configuration).



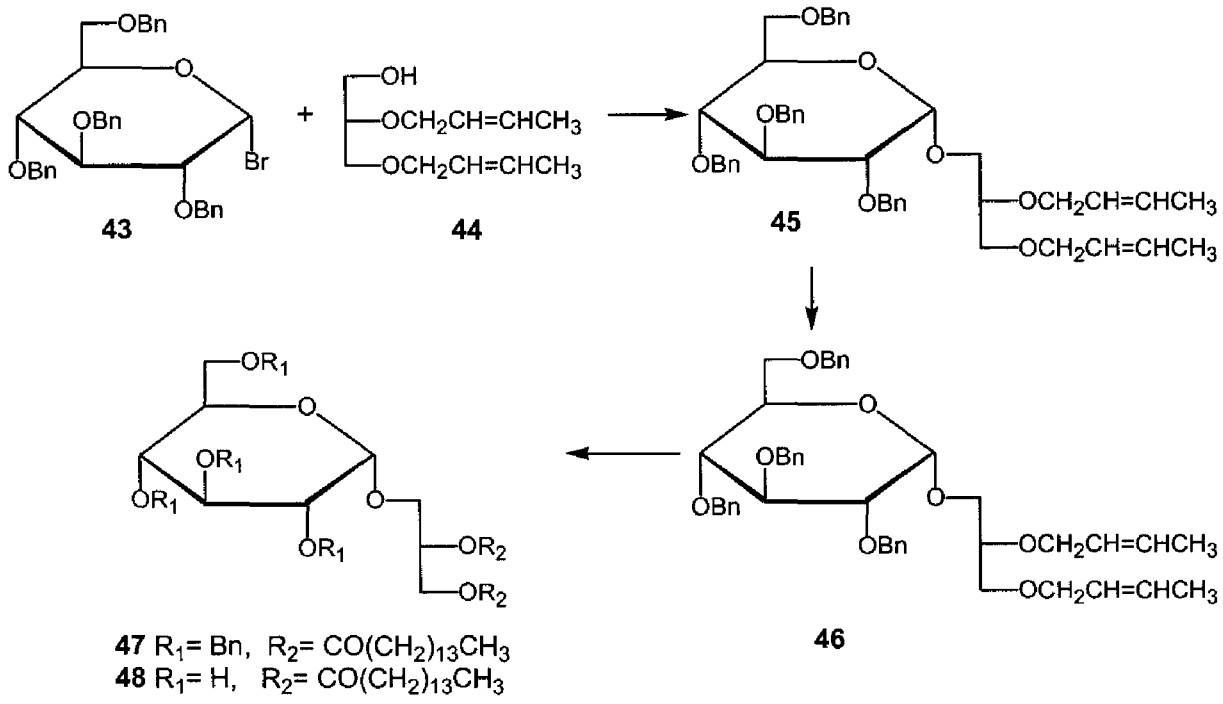
Scheme 2.5: Synthesis of 3-*O*-(β-**D**-glucopyranosyl)-1,2-di-*O*-oleoyl-*sn*-glycerol (**36**)

Gent and Gigg,[28] also reported the synthesis of the acylated derivative **42**. Treatment of 3-*O*-(2',3',4'-tri-*O*-benzyl β-**D**-galactopyranosyl)-*sn*-glycerol (**37**) with acetone in the presence of an acid catalyst, followed by benzylation of the product, gave 3-*O*-(2',3',4',6'-tetra-*O*-benzyl β-**D**-galactopyranosyl)-1,2-*O*-isopropylidene-*sn*-glycerol (**39**). The isopropylidene group of **39** was then removed by acid hydrolysis to give the diol **40** which was acylated with hexadecanoyl (palmitoyl) chloride in pyridine to give the ester **41**. Debenzylation of **41** (hydrogenolysis) yielded 1,2-di-*O*-palmitoyl-3-*O*-(β-**D**-galactopyranosyl)-*sn*-glycerol (**42**). Previously, the synthesis of **42** was achieved by the orthoester method (*vide infra*),[45] and by partial synthesis [46] from natural material.



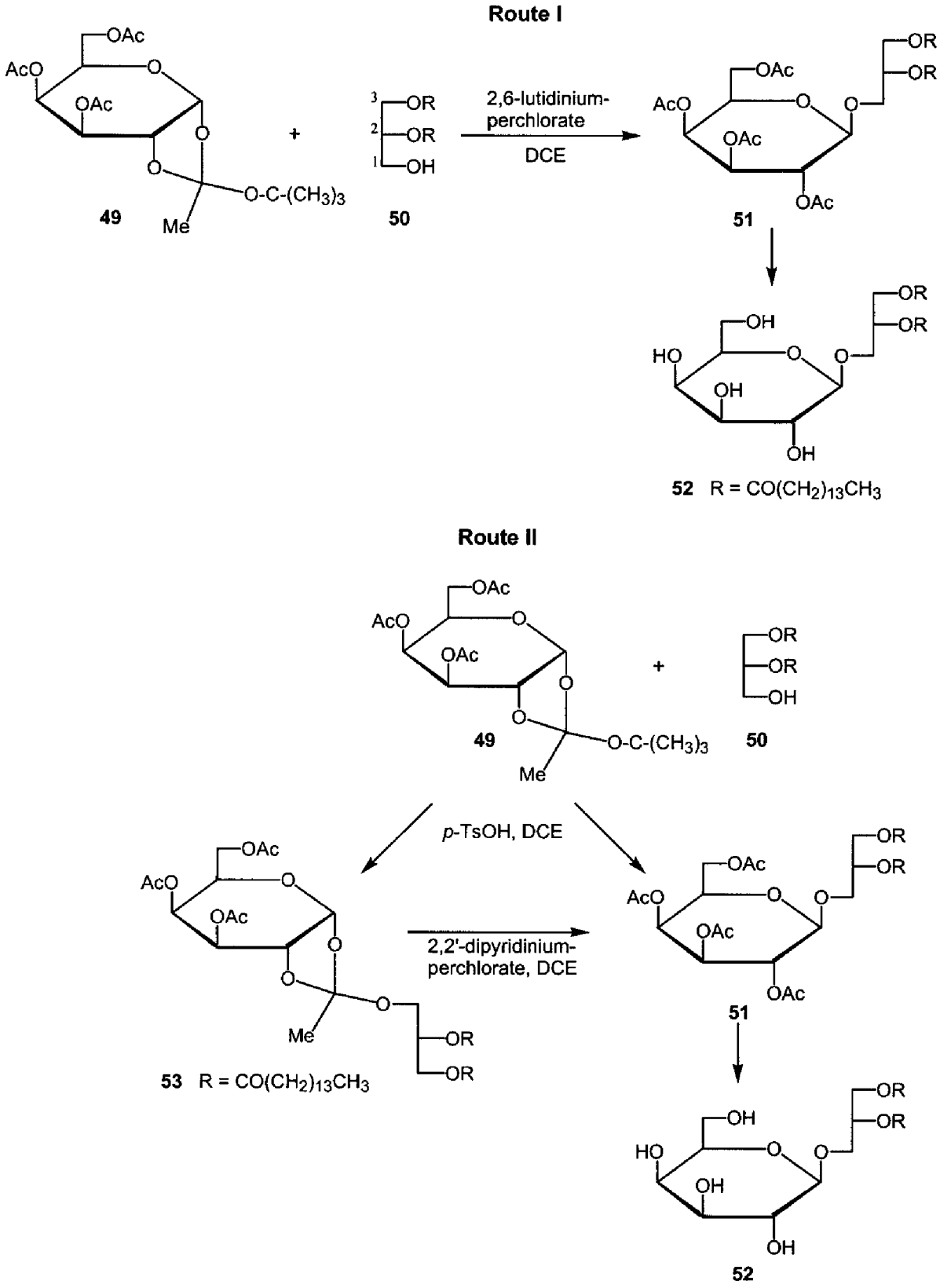
Scheme 2.6: Synthesis of 3-*O*-(β-D-galactopyranosyl) 1,2-di-*O*-palmitoyl-*sn*-glycerol (**42**)

It is well known that optically active 1,2-*O*-isopropylidene-*sn*-glycerol undergoes racemization (*via* acetal migration) [47] under Koenigs-Knorr reaction conditions due to acid catalysed intramolecular migration of the isopropylidene group. Van Boeckel and van Boom, [44] reported the synthesis of the α-D-glucosyl diglyceride **48**, starting from the optically pure and the very stable 1,2-di-*O*-(but-2-enyl)-*sn*-glycerol (**44**) derivative, prepared according to reported methods [48,49] (Scheme 2.7). Compound **44** was condensed with 2,3,4,6-tetra-*O*-benzyl α-D-glucopyranosyl bromide (**43**), [50,51] under conditions described by Lemieux *et al.*[52] to afford 3-*O*-(2',3',4',6'-tetra-*O*-benzyl α-D-glucopyranosyl)-1,2-di-*O*-(but-2-enyl)-*sn*-glycerol (**45**), as a syrup. Removal of the but-2-enyl protecting group was achieved by treatment of **45** with potassium *tert*-butoxide in dimethyl sulfoxide.[33] The two remaining free hydroxyl groups of 3-*O*-(2',3',4',6'-tetra-*O*-benzyl α-D-glucopyranosyl-*sn*-glycerol (**46**) were acylated with palmitoyl chloride to give **47**, which on standard debenzylation (H_2, Pd/C) afforded **48**.



Scheme 2.7: Synthesis of 3-*O*-(α-**D**-glucopyranosyl) 1,2-di-*O*-palmitoyl-*sn*-glycerol (**48**)

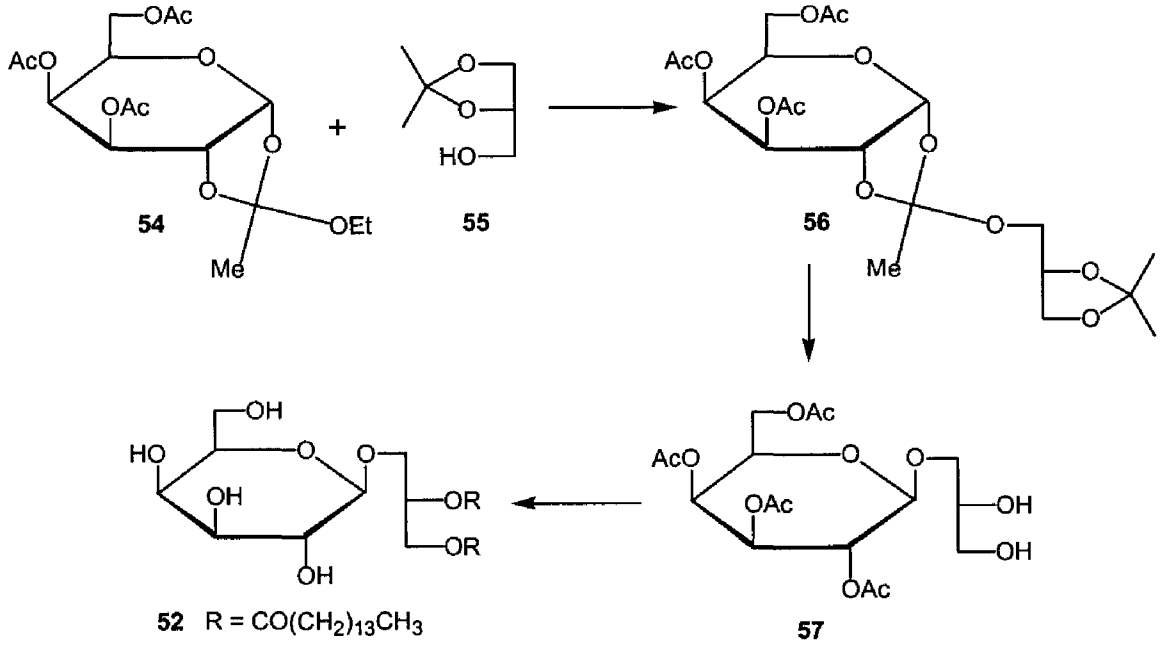
Glycosyl di-ester glycerides can also be prepared using the "orthoester" method.[53] The procedure was employed in the preparation of di-esters from **D**-mannosyl, **D**-glucosyl [54,55] and **D**-cellobiosyl[56] precursors. Bashkatova *et al.*[45] prepared compound **52** starting from the **D**-galactose orthoester **49**, which was obtained by the general method for the preparation of the orthoesters of monosaccharides by treatment of tetra-*O*-acetyl α-**D**-galactopyranosyl chloride with the respective alcohol in the presence of 2,6-lutidine.[53] The 3,4,6-tri-*O*-acetyl-1,2-*O*-*tert*-butyl-*ortho*-acetyl α-**D**-galactopyranose (**49**) so obtained, was then reacted with 1,2-di-*O*-palmitoyl-*sn*-glycerol (**50**) in boiling chlorobenzene in the presence of a catalytic amount of 2,6-lutidinium perchlorate to give **51**. Deacetylation of the hydroxyl groups of the sugar moiety was effected by reaction of **51** with hydrazine hydrate in boiling alcohol (85%) (Scheme 2.8a, Route I). Attempted glycosylation of **49** with the glycerol derivative **50** in boiling dichloroethane in the presence of *p*-toluenesulfonic acid [55] resulted in two products, the glycoside **51** and orthoester derivative **53** (Scheme 2.8a, Route II). The isomerization of the orthoester derivative **53** to compound **51** was achieved by treatment with a catalytic amount of 2,2'-dipyridinium perchlorate in boiling dichloroethane.



Scheme 2.8a: Synthesis of 3-*O*-(β-D-galactopyranosyl) 1,2-di-*O*-palmitoyl-*sn*-glycerol (**52**)

A second approach was investigated for the synthesis of the galactosyl diglyceride **52** *via* the galactosyl glycerol intermediate **57** [45] (Scheme 2.8b). In this case, the starting material was compound **54**. Treatment of 1,2-*O*-isopropylidene-*sn*-glycerol (**55**) with compound **54** in the presence of a catalytic amount of 2,2'-dipyridinium perchlorate in boiling toluene gave 1,2-*O*-isopropylidene-3-*O*-(2',3',4',6'-tetra-*O*-acetyl β-D-galactopyranosyl)-*sn*-glycerol (**56**). However,

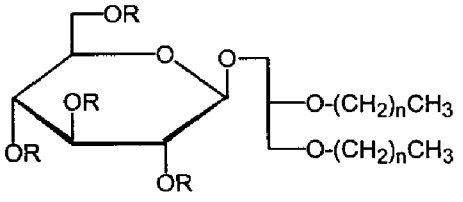
the yield of **56** did not exceed 10% under the various conditions employed. In all cases the reaction favoured the formation of ethyl 2,3,4,6-tetra-*O*-acetyl β-**D**-galactopyranoside.[45]



Scheme 2.8b: Synthesis of 3-*O*-(β-**D**-galactopyranosyl)1,2-di-*O*-palmitoyl-*sn*-glycerol **52** via **57**

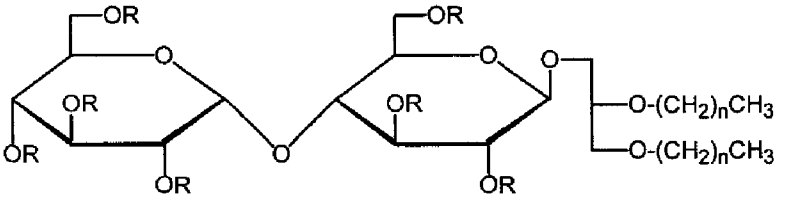
2.5 Synthesis of dialkyl glycosyl-*sn*-glycerols

The synthesis of some long chain 1,2-di-*O*-alkyl-3-*O*-glucosyl-*sn*-glycerols and 1,2-*O*-dialkyl-3-*O*-maltosyl-*sn*-glycerols as model compounds for glycolipids of archaebacteria has been reported.[57] Glycosylation of 1,2-di-*O*-alkyl glycerols [58] with peracetylated **D**-glucose or **D**-maltose in the presence of $SnCl_4$ or trimethylsilyl trifluoromethanesulfonate as catalyst, resulted in complex mixtures which were difficult to purify. It was established that addition of iodine enhanced the rate of the glycosidation reaction under Koenigs-Knorr conditions and suppressed the formation of by-products, especially orthoesters.[59] The glycosidation reaction was then carried out using a 1,2-di-*O*-alkyl glycerol derivative with acetobromoglucose or acetobromomaltose in the presence of I_2 / Ag_2O / powdered molecular sieve (4Å) in absolute benzene. The peracetylated 1,2-di-*O*-alkyl-3-*O*-**D**-glycosyl-*sn*-glycerols **58-60** and **61-63** were obtained after 20 hr. Deacetylation using 0.05**M** sodium methoxide in absolute methanol gave the 1,2-di-*O*-alkyl-3-*O*-β-**D**-glycosyl-*sn*-glycerols **64-66** and **67-69**.[57]



58 n=13, R=Ac
59 n=15, R=Ac
60 n=17, R=Ac

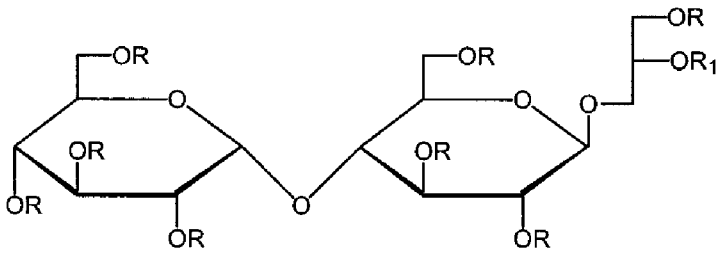
64 n=13, R=H
65 n=15, R=H
66 n=17, R=H



61 n=13, R=Ac
62 n=15, R=Ac
63 n=17, R=Ac

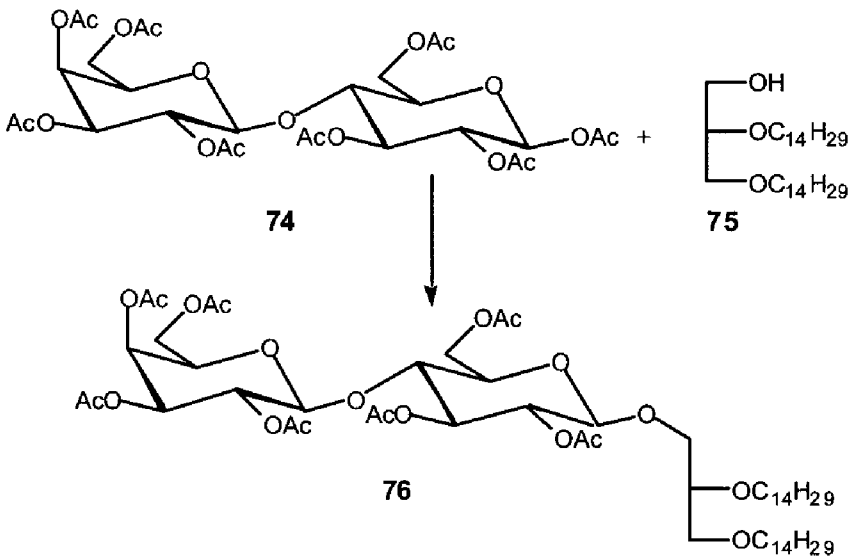
67 n=13, R=H
68 n=15, R=H
69 n=17, R=H

Using a similar synthetic approach, Prinz *et al.*[60] succeeded in the stereoselective synthesis of various long chain 1-*O*-(β-D-maltosyl)-3-*O*-alkyl-*sn*-glycerols (**70-73**). These compounds represent examples of alkyl glyceryl ether glycolipids. There was not much difference in some physical properties (e.g. critical micelle concentration and haemolytic activity) of these amphiphilic derivatives. Other properties, such as anti-tumour activity, differed considerably from those of analogues with a zwitterionic phosphorylcholine head group.



70 R=H; R_1=CH_3-$(CH_2)_{11}$
71 R=H; R_1=CH_3-$(CH_2)_{13}$
72 R=H; R_1=CH_3-$(CH_2)_{15}$
73 R=H; R_1=CH_3-$(CH_2)_{17}$

Lewis acids have also been employed as efficient catalysts for the activation of the anomeric position of suitable sugar derivatives for the formation of alkylated glycerol derivatives with 1,2-*trans*-glycosidic linkages. Treatment of an equimolar mixture of octa-*O*-acetyl β-D-lactose (**74**) with derivative **75** in 1,2 dichloroethane, in the presence of an equivalent amount of trimethylsilyl trifluoromethanesulfonate and molecular sieve (4 Å), afforded the β-D-glycoside **76**, isolated in 70% yield (Scheme 2.8c).[61]

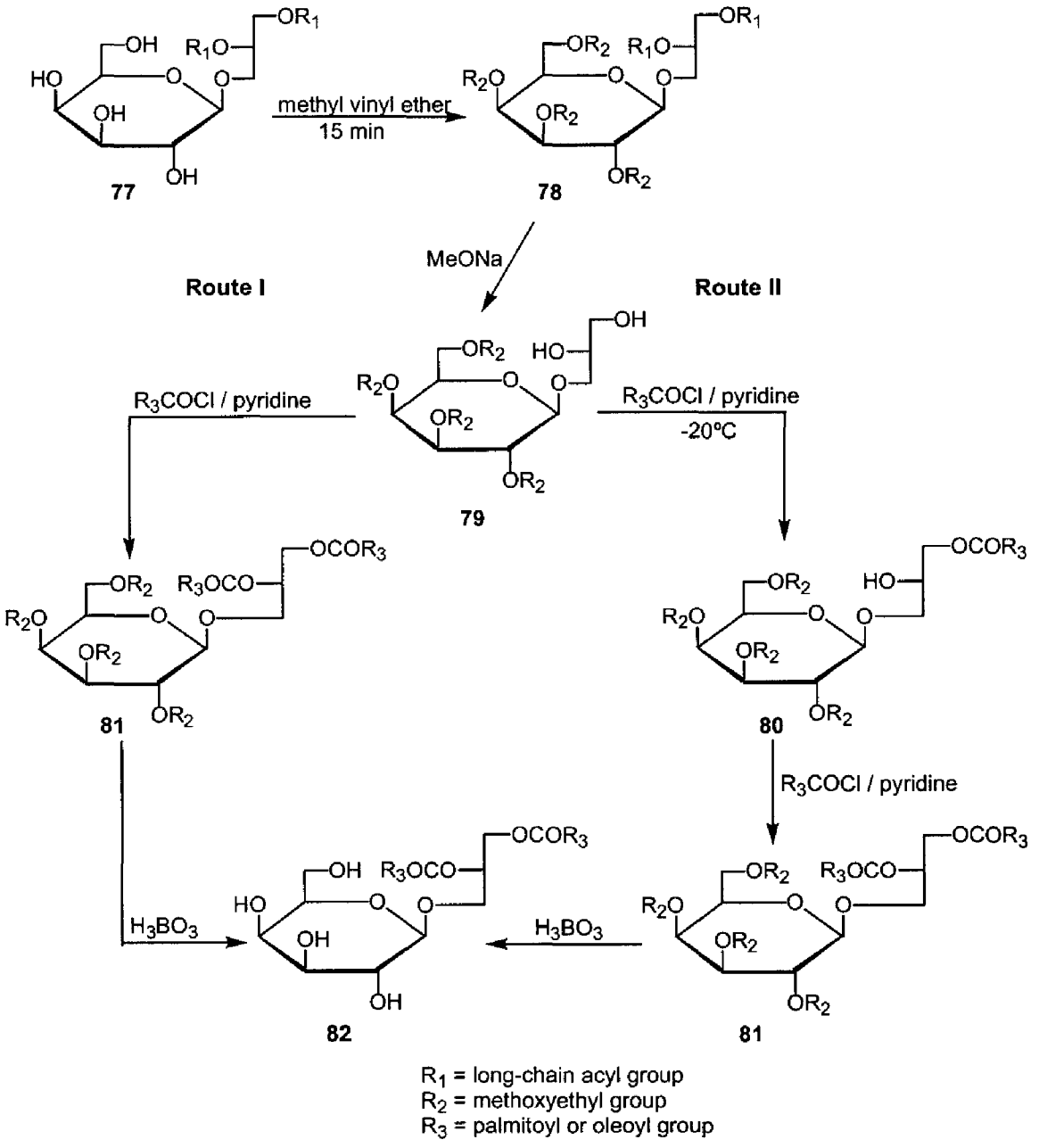


Scheme 2.8c: Synthesis of the β-D-glycoside **76**

2.6 Semi-synthesis of glycosyl diglycerides

Attempts have also been made to obtain mono- and digalactosyl diglycerides having identical or different acyl groups attached to C-1 and C-2 of the glycerol moiety starting from natural lipids using 1'-*O*-methylethoxy ether groups as *O*-protecting functions. [62] The starting materials were naturally occurring galactolipids extracted from *Sinapsis alba* and *Spinacia oleracea* leaves. Treatment of the mono galactosyl diglyceride, 1,2-di-*O*-acyl-3-*O*-β-D-

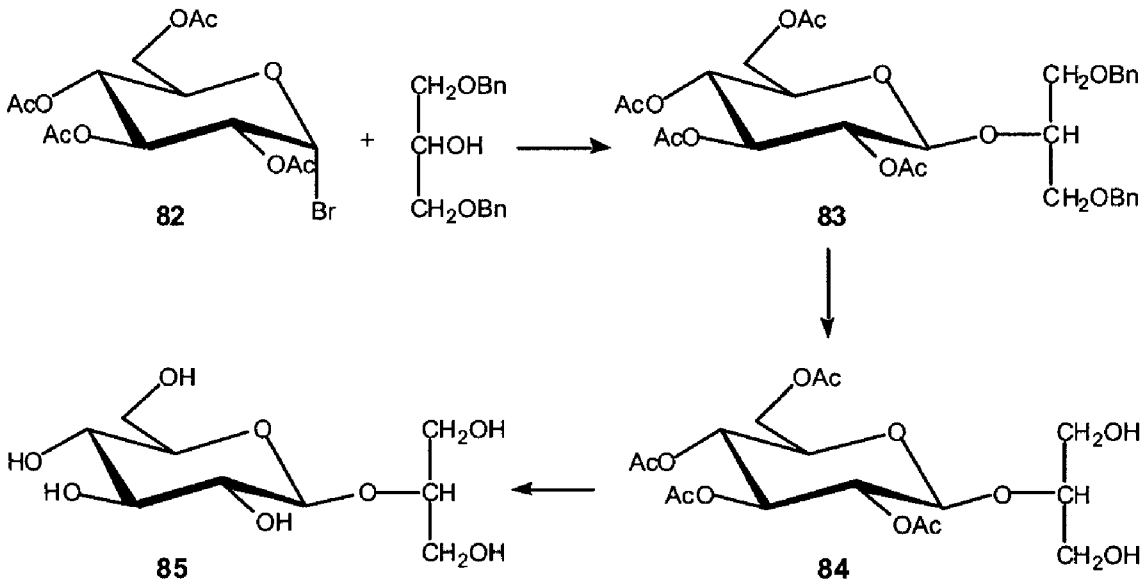
galactopyranosyl-*sn*-glycerol (**77**) with methyl vinyl ether in the presence of *p*-toluenesulfonic acid gave 1,2-di-*O*-acyl-3-*O*-[2',3',4',6'-tetra-*O*-(1"-methoxyethyl)-β-**D**-galactopyranosyl]-*sn*-glycerol (**78**) (Scheme 2.9). Removal of the acyl residues on the glycerol moiety in **78** by reaction with sodium methoxide yielded the intermediate product, 3-*O*-[2',3',4',6'-tetra-*O*-(1"-methoxyethyl)-β-**D**-galactopyranosyl]-*sn*-glycerol (**79**) which was used for the subsequent reactions. The obtained compound **79** was acylated with fatty acid chlorides at room temperature (Route 1) to yield compound **81**. When the reaction was performed at –20°C with a controlled quantity of acylating agent (Route II) selective reaction occurred at the primary position to give compound **80**. This material could then be acylated to give the di-ester **81** with different acyl groups at C-2 (Scheme 2.9).[62]



Scheme 2.9: Synthesis of 1,2-di-*O*-acyl-3-*O*-(β-**D**-galactopyranosyl)-*sn*-glycerols

2.7 Synthesis of 2-*O*-β-D-glycosyl glycerols

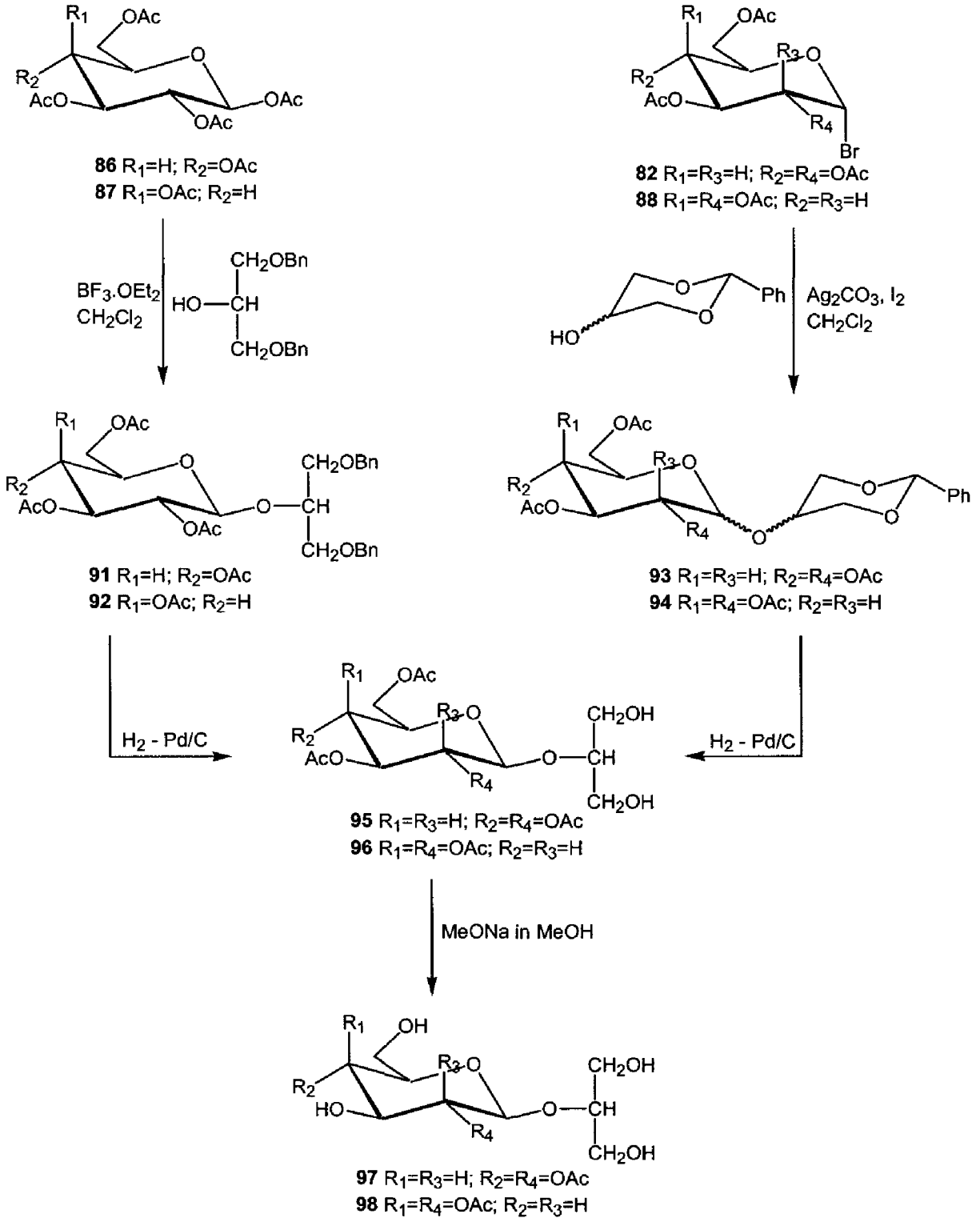
The synthesis of these sugar derivatives usually involves variations of the classical Koenigs-Knorr reaction, i.e. treatment of a glycosyl halide with an alcohol in the presence of heavy metal salts or an organic base as the acid acceptor. The reaction proceeds with inversion of configuration at the anomeric carbon atom. The simple synthesis of glucosyl glycerols has been described to obtain products which occur naturally in bulbs of the genus *Lilium*.[63-65] In the course of synthesizing these compounds, a simple variation of the Koenigs-Knorr reaction was sought.[66] Thus, 2,3,4,6-tetra-*O*-acetyl α-**D**-glucopyranosyl bromide (**82**) was reacted at room temperature with 1,3-dibenzyloxy-2-propanol in dry acetonitrile in the presence of $Hg(CN)_2$, and $HgBr_2$ as catalyst to give the crystalline compound **83** in 67% yield (Scheme 2.10). Removal of the benzyl groups on **83** by catalytic hydrogenolysis (10% Pd/C) at room temperature afforded the crystalline diol **84**. Deacetylation of **84** with sodium methoxide in methanol at room temperature, followed by treatment with Amberlite-IR-120 ion-exchange resin (H^+ form) gave the unsubstituted glucosyl glycerol **85**. The C-2 position of the glycerol unit in these derivatives is not chiral unless there are two different ester (or alkyl) groups on each of the two primary hydroxyl positions of the glycerol moiety.



Scheme 2.10: Synthesis of 2-*O*-β-D-glucopyranosyl glycerol (lilioside B)

The preparation of the 2-*O*-linked glycerol compounds, *e.g.* **97** and **98,** have also been reported.[18] The first synthetic approach involved the use of the 1,3-di-*O*-benzyl glycerol aglycon,[67] which is stable in the presence of Lewis acids, i.e. boron trifluoride-etherate which was used as a catalyst for condensation with the sugar peracetates.[68] Under these conditions, the 1,3-di-*O*-benzyl-2-*O*-(2',3',4',6'-tetra-*O*-acetyl β-**D**-glycopyranosyl)-glycerol derivatives **91** and **92** of **D**-glucose, and **D**-galactose respectively, were obtained in reasonable yield, with exclusive formation of the β-products (Scheme 2.11).[66] Catalytic hydrogenolysis (H_2, Pd/C) yielded compounds **95** and **96**, which on treatment with methanolic sodium methoxide gave the targets **97** and **98**. The formation of the α-products was not observed. It is known that use of Lewis

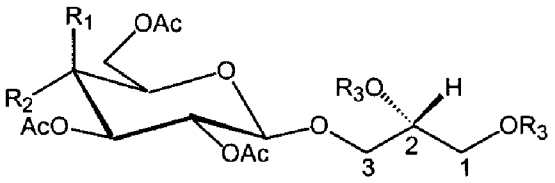
acids as catalyst can lead to anomeric mixtures. In a second approach,[18] which was aimed at obtaining compounds **95** and **96**,[69] an *endo* / *exo*-mixture of 2-phenyl-5-hydroxy-1,3-dioxolan (1,3-*O*-benzylideneglycerol) (**90**) [70,71] was used as the aglycon. The Koenigs-Knorr reaction was utilized since this glycerol derivative is quite sensitive towards Lewis acids. The yields of intermediates **93** and **94** formed during the condensation reactions were quite low (20-30%). Catalytic hydrogenolysis followed by treatment with base gave **97** and **98** (Scheme 2.11).



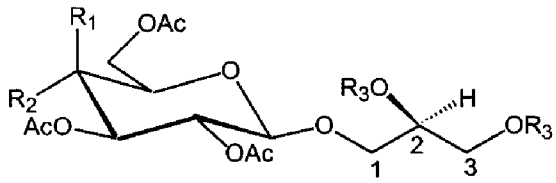
Scheme 2.11: Synthesis of 2-*O*-β-D-(glycopyranosyl) glycerols

2.8 The use of enzymes in the formation of glycosyl glycerols and related compounds

It is well known that lipases can be used for the resolution of racemic mixtures of alcohols[72] as well as in regio- and diastereoselective acylation of sugars.[73] Enzymatic induced transesterification reactions have been carried out in organic solvents using *Pseudomonas cepacia* (LPS) in the separation of diastereoisomeric mixtures of glycosyl derivatives to obtain optically pure 1-*O*- and 3-*O*-D-glucosyl- and D-galactosyl-*sn*-glycerols. 1-*O*/3-*O*-(2',3',4',6'-tetra-*O*-acetyl β-D- glucopyranosyl)-*sn*-glycerols **98** and **99**, and 1-*O*/3-*O*-(2',3',4',6'-tetra-*O*-acetyl β-D-galactopyranosyl)-*sn*-glycerols **100** and **101** were selected in protected forms so as to avoid any possible acylation of the glycosyl subunits.[74] The results obtained from these reactions indicated that the faster reacting diastereoisomers were the 3-*O*-*sn*-glycerol derivatives **98** and **100** but were, however, obtained only with moderate diastereoisomeric excess using these transesterification reactions. The effects of solvents used in the reactions were also investigated, and it was found that when the reactions were performed in chloroform higher selectivity in the case of glucosyl derivatives **98** and **99** was observed, whilst for galactosyl derivatives **100** and **101**, the selectivity remains unchanged.[75] The selectivity in chloroform for galactosyl derivatives **100** and **101** was increased by lowering the temperature of the process to 0°C.



98 R_1=H, R_2=OAc, R_3=H
100 R_1=OAc, R_2=H, R_3=H

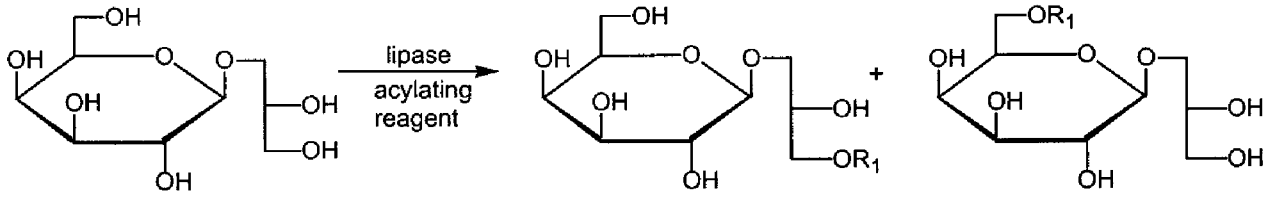


99 R_1=H, R_2=OAc, R_3=H
101 R_1=OAc, R_2=H, R_3=H

2.9 Enzymatic approach to the synthesis of mono- and diester derivatives of glycosyl glycerols

The ability of suitable enzymes to catalyze regioselective or stereoselective acylation of the glycerol portion with various activated long-chain carboxylic acid esters as acyl donors has resulted in the generation of products that exhibit interesting biological activities including anti-inflammatory and anti-HIV activity. In the enzymatic acylation reactions reported, the regioselectivity in most cases depended on the differences in the reactivity of the primary and secondary hydroxyl groups of the substrate.[11] Lipase catalyzed regioselective acylation reactions were carried out with 3-*O*-(β-D-galactopyranosyl)-*sn*-glycerol (**102**) (Scheme 2.9a). Several lipases were screened using vinyl palmitate [76] as the acylating agent. The acylation of **102** proceeded only slightly in *N,N*-dimethyl formamide or dimethyl sulfoxide, and gave only trace amounts of diesters in tetrahydrofuran. When pyridine was used as the reaction medium, a mixture of monoesters **103a-f** and **104a-f** was obtained, in which the acyl residues were linked only to the primary hydroxyl groups.[11] Other palmitate donors such as the trichloroethyl, trifluoroethyl and isopropenyl esters were also screened, but all exhibited reactivities lower than

vinyl palmitate. It is noteworthy that compound **103g** containing a linoleic residue, which is susceptible to oxidation, was obtained in nearly the same yield as the other derivatives.



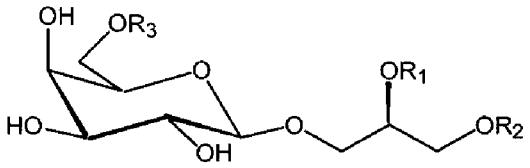
102

103a R_1= palmitoyl
103b R_1= lauroyl
103c R_1= myristoyl
103d R_1= palmitoleatoyl
103e R_1= stearatoyl
103f R_1= oleoyl
103g R_1= linoleoyl

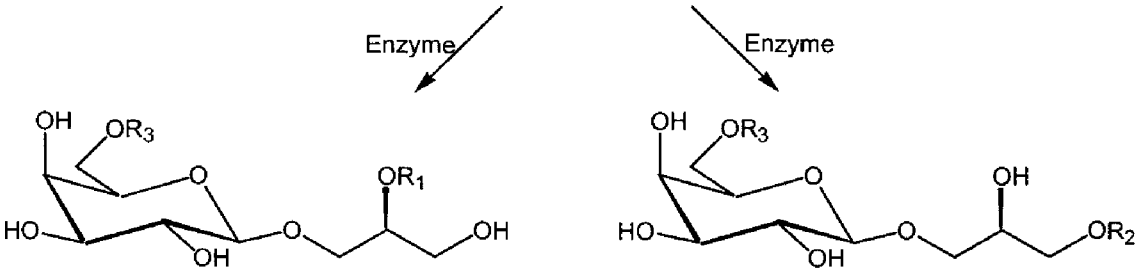
104a R_1= palmitoyl
104b R_1= lauroyl
104c R_1= myristoyl
104d R_1= palmitoleatoyl
104e R_1= stearatoyl
104f R_1= oleoyl
104g R_1= linoleoyl

Scheme 2.9a: Lipase catalyzed acylation reactions of 3-*O*-(β-D-galactopyranosyl)-*sn*-glycerol **102**

Similar treatment of the monogalactosyl and the galactosyl diacylglycerols **105** and **106** with a lipase from *Rhizopus arrhizus* in boric acid / borax buffer afforded compounds **107** and **108** [77,78] exclusively (Scheme 2.9b). When the reaction was performed in tris-buffer alone, the regioselectivity was completely reversed, and compounds **109** and **110** were then the sole products (Scheme 2.9b).



105 R_1=linolenoyl, R_2=myristoyl, R_3=H
106 R_1=linolenoyl, R_2=myristoyl, R_3=α-galactopyranosyl



107 R_1=linolenoyl, R_3=H
108 R_1=linolenoyl, R_3=α-galactopyranosyl

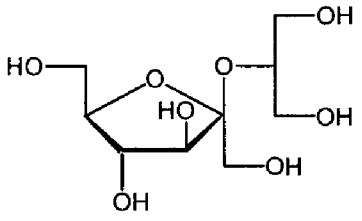
109 R_2=myristoyl, R_3=H
110 R_2=myristoyl, R_3=α-galactopyranosyl

Scheme 2.9b: Lipase catalyzed acylation reactions of galactosyl glycerols **105** and **106**

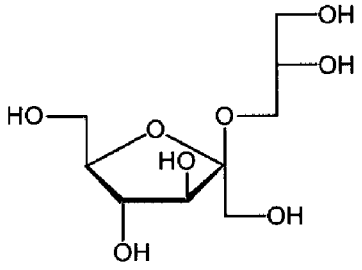
2.10 Enzymatic synthesis of fructosyl glycerols

Levansucrases (EC 2.4.1.1) are enzymes known for their transfructosylase activity to produce levans.[12] However, under particular reaction conditions these enzymes can transfer D-fructose to other nucleophiles, thereby producing oligosaccharides from mono- or disaccharides.

Levansucrase from *Bacillus subtilis* has the ability to transfer D-fructose to sugars such as D-glucose, D-xylose, L-arabinose, D-galactose, melibiose and D-lactose.[79] Levansucrase from *Rhahnella aquatilis* has also been successfully used in the synthesis of oligosaccharides using mono- and disaccharides as acceptors. The enzyme was found incapable of transferring D-fructose to sugar alcohols such as D-xylitol, D-sorbitol or D-maltitol. The transfer of sugars from oligosaccharides to glycerol using various enzymes has been achieved, but in very low yield.[80] The ability of a levansucrase from *Bacillus circulans* to transfer a D-fructose unit to glycerol, albeit in low yield, was reported recently.[81] The low yields were due to hydrolysis and the concurrent levan-synthesizing activities of the enzyme preparation. Gonzalez-Munoz *et al.*[12] have also reported the enzymatic synthesis of two fructosyl-glycerol derivatives, **111** and **112** using levansucrases isolated from *B.subtilis* and *B.circulans*, with sucrose acting as the fructosyl donor. These authors seem to be confused over the nomenclature / structure relationship of D-fructose compounds. They consistently term their products as pyranose derivatives but present structural formulae in the furanose form. The ^{13}C-NMR data suggests that the products are present in the furanose form as depicted. The effect of reaction conditions on the relative hydrolase and transferase activities of the enzymes were also studied. It was observed that in aqueous solutions of sucrose, more than 50% of the enzyme activity was hydrolytic, producing D-glucose and D-fructose, whereas the rest of the activity was involved in the transfer of D-fructose to the growing D-fructose polymer (levan) chain. The hydrolytic effect was reduced by the addition of glycerol which was also an acceptor for the transferred D-fructose units. Very low hydrolytic activities were observed when 50% of glycerol was used in the reaction mixtures. Under these conditions, the hydrolysis was reduced to a minimum level and, as a result, 78% of D-fructose was transferred to glycerol and the remaining material was found as free D-fructose, in levans, or as traces of by-products with high retention times on HPLC. All compounds in the mixture were separated by preparative HPLC and the yields of **111** and **112** were 38% and 40%, respectively. The enzyme seems to have only a slight preference for the C-1 and C-3 hydroxyl groups in glycerol over the secondary hydroxyl at C-2. No evidence was presented for possible diastereoselectivity in the formation of **112**.



111



112

In the forthcoming chapters attempts to obtain specific glycerol derivatives of D-fructose using chemical synthesis will be presented. The formation of some nitrogen-containing analogues including, aziridines, hydroxyl-amides, and long-chain acylated derivatives thereof will also be described.

2.11 References

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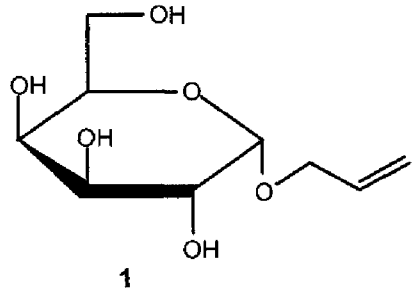
CHAPTER 3

SYNTHESIS OF 2,3-DIHYDROXYPROPYL β-D-FRUCTOPYRANOSIDE (FRUCTOSYL GLYCEROL) AND RELATED COMPOUNDS FROM D-FRUCTOSE

3.1 Introduction

Glycosyl glycerols and their derivatives (glyceroglycolipids) are an important class of organic compounds widely distributed in nature. Attention towards these compounds is increasing due to the biological activities shown, in particular, by compounds in which the sugar moiety is β-linked to the primary position of glycerol derivatives.[1] The isolation of these compounds from natural sources is cumbersome, and only small amounts are usually obtained. Consequently, the development of new efficient synthetic methods for the preparation of these compounds is becoming a timely challenge in the field of synthetic chemistry and biochemistry, for use in biomedical research (see Chapter 2). There are two main procedures which have been employed for the syntheses of these products in diastereomerically pure forms. These are the coupling of a glycosyl moiety with optically pure glycerol derivatives,[2] or reaction with a racemic glycerol derivative, followed by conventional or enzymatic separation of the diastereomeric mixture of products.[3]

A simple approach for obtaining glycosyl glycerol derivatives involves the oxidation of the double bond in allyl glycosides.[4] The synthesis of allyl β-D-glycosides can be carried out by the reaction of unprotected sugars with allyl alcohol saturated with dry hydrogen chloride gas or from suitably protected and activated derivatives using Koenigs-Knorr type procedures.[4,5] A synthesis of racemic isofloridoside **2** was effected from the galactoside **1** by oxidation of the double bond using *m*-chloroperbenzoic acid, followed by acid catalyzed opening of the resultant diastereomeric mixture of oxiranes, and removal of the protecting groups. The final yield of **2** was not cited but a combined yield of 60% was obtained for the two preceding steps.[4]



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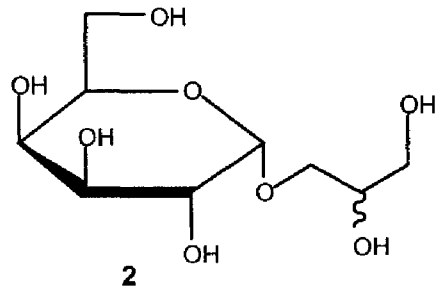

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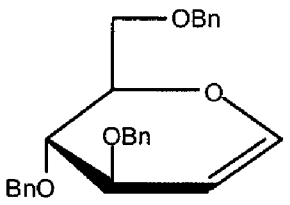
The synthesis of allyl β-D-glycosides has also been performed using other types of protected glycosyl donors. Allyl β-D-glucopyranoside (**6**) was obtained as the major product in a series of reactions which involved the intermediate formation of oxiranes **4** and **5** from the

glucal **3**. Treatment of **4** and **5** with allyl alcohol gave a mixture of **6** and **7** in the ratio of 90:10, respectively. The drawback of the synthetic methods discussed above is the possible formation of diastereoisomeric mixtures of two anomeric products (α and β) which cannot always be separated by column chromatography or selective crystallization.[6] Koenigs-Knorr or Schmidt type procedures usually lead to specific products, but these approaches cannot be used with **D**-fructose (see Chapter 1).



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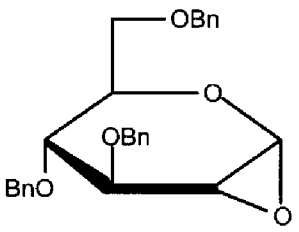

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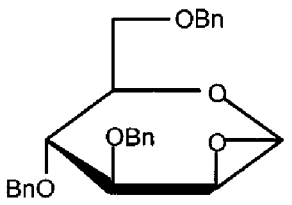

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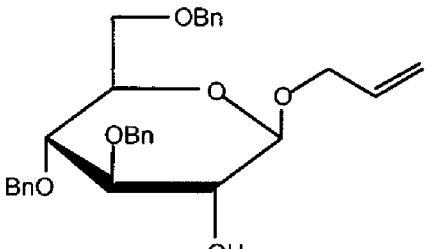

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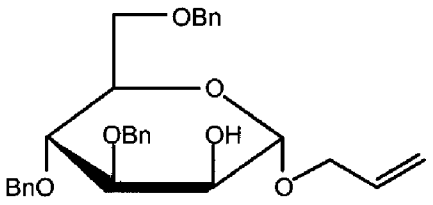
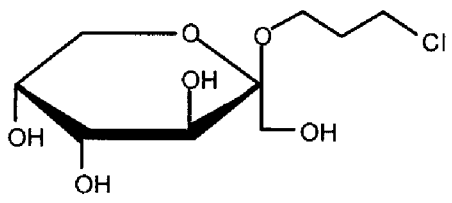


7

Compound **9** and its derivative **10**, are of great potential interest for the preparation of hitherto unknown 2,3-dihydroxypropyl β-**D**-fructopyranosides. The allyl β-**D**-fructopyranoside (**9**) is one of the relatively few, easily obtainable, crystalline fructosides that have been reported.[7] It is prepared in 40-45% yield by treatment of **D**-fructose with allyl alcohol containing *ca* 1% hydrogen chloride. It is also obtained as a major product when the chloropropyl derivative **8** is treated with potassium *tert*-butoxide in *N,N*-dimethylformamide and in minor amounts when **8** is reacted with sodium butoxide, or sodium hydroxide in ethanol.



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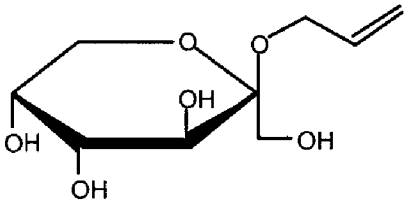

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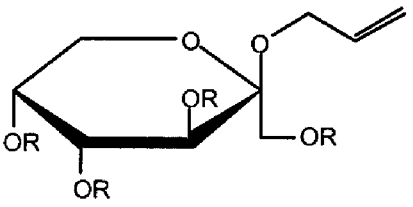
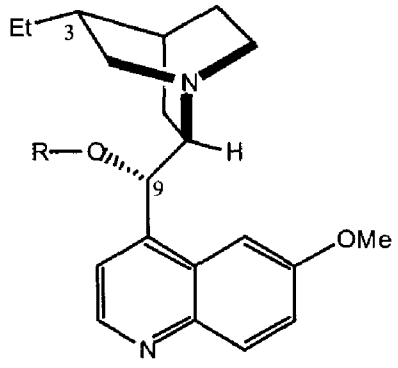


10

R= Ac

There are several methods available to achieve the dihydroxylation of olefins and most of them rely on osmium tetroxide oxidations. Osmium-catalyzed asymmetric dihydroxylation reactions (Sharpless type) have provided powerful selective synthetic methods to introduce oxygen functionalities onto olefins. These synthetic approaches have been enhanced by introduction of chiral nitrogen-containing ligands which have greatly improved the efficacy of asymmetric dihydroxylation reactions. In general, chiral ligands based on dihydroquinine

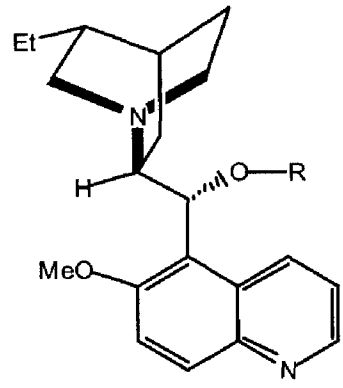
(DHQ) (**11**) and dihydroquinidine (DHQD) (**12**) skeletons are employed in these type of reactions. Compounds **11** and **12** are minor components of the naturally occurring cinchona alkaloids. Apart from these chiral ligands, there are very few other catalytic systems which have been used in asymmetric dihydroxylations.[8,9,10a-d] Dihydroquinine **11** and dihydroquinidine **12** become very effective ligands for asymmetric dihydroxylation when they are derivatized at the C-9 hydroxyl group. In their role as chiral ligands these derivatives, in most cases, function almost as if they are enantiomers, although they are actually diastereoisomers due to differences in the attachment of the ethyl group. A wide range of applications for the enantioselective asymmetric dihydroxylation of prochiral olefins including allyl ethers [11] and esters [12] has been reported, but the asymmetric dihydroxylation of chiral allyl ethers is less well documented. There are few examples of the application of these reactions to alkenyl derivatives of carbohydrates.



11

Dihydroquinidine (R=H)

(DHQD)



12

Dihydroquinine (R=H)

(DHQ)

3.2 Results and discussion

3.2.1 Synthesis and reactions of allyl β-D-fructopyranoside (9)

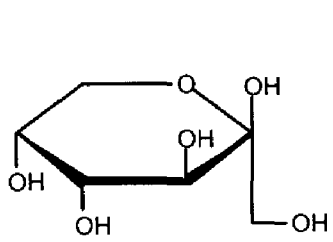
For the proposed synthesis of fructosyl glycerols and other related compounds, allyl β-D-fructopyranoside **9** was considered to be a suitable starting material, which can be prepared from **13** according to the reported procedure.[7] Although the glycoside **9** is asymmetric the chiral centres of the fructosyl moiety are probably too distant from the reacting double bond to influence the diastereofacial selectivity of a reaction on the terminal olefin. In connection with the syntheses of these derivatives, an appropriate synthetic approach was required to achieve this selectivity on the terminal olefin. It was expected that, among other approaches which were to be considered, asymmetric dihydroxylation (Sharpless type) reactions would be the most likely method to give satisfactory results. Compound **9**, which is water soluble could react in the aqueous phase when subjected to the oxidation reactions. Catalytic asymmetric dihydroxylations are two phase reactions, and due to this fact it was also considered necessary to convert the remaining hydroxyl groups into suitably protected functions which would lower the solubility of

9 in the aqueous phase, thus enhancing selectivity, and which could be removed easily at a later stage.

The protection of hydroxyl groups with 1-*O*-ethoxyethyl protecting functions has been suggested to be useful in synthetic carbohydrate chemistry.[13] These protecting groups are very stable under strong basic conditions and can also be removed in the presence of other acetals under mild acidic conditions. Treatment of a solution of **9** in 1,2-dimethoxyethane with ethyl vinyl ether in the presence of pyridinium-*p*-toluenesulfonate (PPTS) yielded compound **14** in almost quantitative yield. This product was troublesome to characterize physically since ethoxyethylation produces a complex mixture of diastereoisomeric products. It is usually considered to be a rather transient protecting function and is removed immediately after the chosen reaction to facilitate characterization of the product. Preliminary reactions of the product **14** were carried out to investigate selectivity in oxidation reactions. The conversion of **14** in acetone / water mixture using potassium permanganate as an oxidizing agent gave a racemic mixture of diols **15** after one hour (TLC) in 98% yield. The stereoselectivity of the reaction was determined by GLC analysis of the peracetyl derivatives of the obtained diols. These were obtained by acetylation of the hydroxyl groups of the aglycon moiety, followed by removal of the ethoxyethyl groups under mild acidic conditions, and subsequent acetylation of this product. The diastereoisomeric excess (d.e) value of the diols obtained from this oxidation reaction was only 22%. This reaction which was performed in the absence of the chiral ligands, clearly indicated poor selectivity.

It was then decided to extend this investigation to the use of compound **10** under similar reaction conditions. Acetylation of compound **9** in the usual manner with acetic anhydride / pyridine mixture gave the tetra-acetate **10** in excellent yield (97.2%). Treatment of **10** in aqueous acetone with a solution of potassium permanganate yielded the crystalline diol **16** (55%). The product obtained was characterized by treatment with *p*-nitrobenzoyl chloride in pyridine solution at room temperature to give compound **17** (77%) as an amorphous solid. The stereoselectivity analysis performed on peracetyl derivatives of the obtained diols showed an improvement in d.e value (50%).

Alternatively, compound **14** was treated with potassium osmate (VI) dihydrate and $K_3[Fe(CN)_6]$, acting respectively as oxidant and co-oxidant, to generate OsO_4. This catalytic asymmetric reaction (Sharpless type) was carried out in the presence of chiral ligands, $(DHQD)_2PHAL$ and $(DHQ)_2PHAL$. Reaction of **14** in the presence of $(DHQD)_2PHAL$ and $(DHQ)_2PHAL$ gave the diols **15** in excellent yields (95-98%). A slight improvement in d.e value (51%) of the diols derived from the asymmetric dihydroxylation reaction, performed using the chiral ligand $(DHQD)_2PHAL$, was observed. Surprisingly, the d.e value of the diols obtained in an asymmetric dihydroxylation reaction carried out using $(DHQ)_2$ PHAL as a chiral ligand, was only 6%. These values were not considered to be sufficiently high to warrant further investigations with the ethoxyethyl group as a protecting function for the fructose ring hydroxyls. No attempts were made to prepare the diols **16** from the catalytic asymmetric reaction (Sharpless type) on compound **10**.



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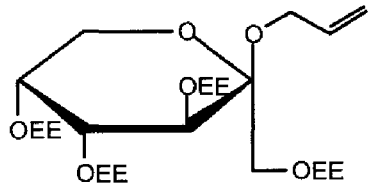
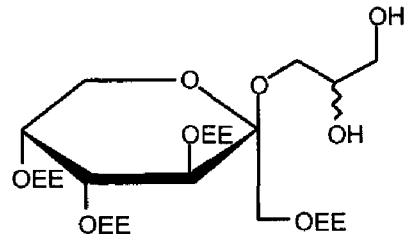
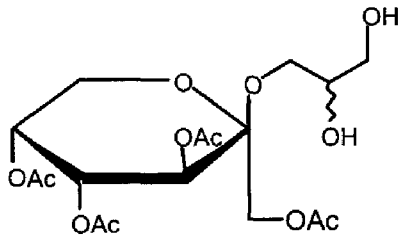


14

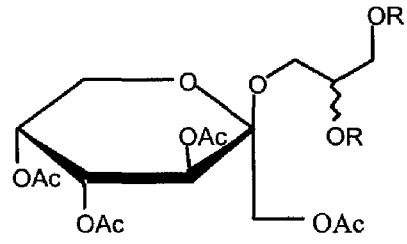


15

EE= ethoxy ethyl



16



17

R= *p*-nitrobenzoyl

Wide use of the *O*-benzyl ether group as a protecting function has been made in synthetic chemistry,[14] particularly with carbohydrate compounds.[15] More recently, the *O*-benzyl ether function has been known to enhance diastereoselectivity of the asymmetric dihydroxylation (Sharpless type) of allyl β-**D**-xylosides. [16] This protecting group is employed frequently because of its ease of introduction during protection sequences, its inherent stability, and the variety of methods available for regenerating the original hydroxyl groups.[17a-c] Catalytic or chemical hydrogenolysis is mostly frequently employed for debenzylation under mild conditions. Benzylation of compound **9** in dimethyl sulfoxide was performed in the usual manner using benzyl chloride in the presence of powdered potassium hydroxide. The crude product was purified by column chromatography to give **18** (79.3%) as colourless oil.

The importance of the chiral ligand structure in asymmetric dihydroxylations has been discussed.[18] The chiral ligands based on phthalazine (PHAL), e.g. $(DHQD)_2PHAL$ and $(DHQ)_2PHAL$, [19] pyrimidine-based (PYR) and anthraquinone-based (AQN) were investigated for their effects on the stereoselectivity in the catalytic asymmetric dihydroxylation reactions (Sharpless type) of compound **18**. The stereoselectivity of the asymmetric dihydroxylation reactions of **18** in the presence of the above mentioned chiral ligands was established by transformation of the product **19** into the corresponding hexaacetyl derivative which involved catalytic debenzylation (H_2, Pd/C) of the obtained product, followed by acetylation of the resultant material in the usual manner (acetic anhydride / pyridine). The acetylated mixtures were then investigated by GLC to establish the respective d.e values (*vide supra*).

Generally, the diastereoisomeric excess values of the diol **19** obtained increased significantly when the *O*-benzyl ether group was used as a protecting function. This increase may be attributed to stacking interactions between the aromatic rings of the *O*-benzyl ether groups with those of catalyst, which can contribute to the correct orientation of the substrate in

the catalytic centre.[16] However, the above hypothesis was not consistent with the results obtained in the asymmetric dihydroxylation of compound **25** in which the aromatic rings were replaced by cyclohexyl rings as protective groups.[16] The observed improvements could also be attributed to favourable hydrophobic interactions [20] between the protecting groups and the catalyst. The steric hindrance between these bulky groups, which tends to favour one orientation of the substrate in the catalytic center, can also be considered as a contributing factor.

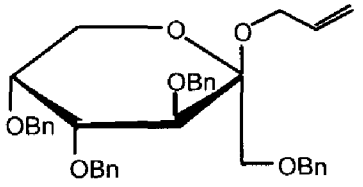
The pyrimidine ligands, specifically $(DHQ)_2PYR$, led to good results in reactions at room temperature, and at 0°C (Table 1, entry 3 and 4). Interestingly, the dihydroquinine based pyrimidine ligand, $(DHQ)_2PYR$, gave products with higher diastereomeric excesses than the corresponding dihydroquinidine, $(DHQD)_2PYR$. These results are not in agreement with previous observations which showed that the $(DHQD)_2PYR$ based-reagent is superior in most cases during asymmetric dihydroxylation reactions of terminal olefins.[21] The dihydroquinidine-based anthra-quinone ligand $(DHQD)_2AQN$ and phthalizine ligand $(DHQD)_2PHAL$ (Table 1, entry 5, 6, and 9) showed only moderate increases in diastereoselectivities. A reduction in d.e values was, in most cases, observed in asymmetric dihydroxylation reactions performed with DHQ ligands.

Table 1: *Asymmetric dihydroxylation of **18** using various chiral ligands*

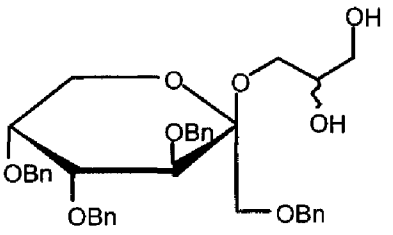
Entry	Ligand	Temp.°C	d.e. (%)	Yield (%)
1	$(DHQD)_2PYR$	22	55.6	82.2
2	$(DHQD)_2PYR$	0	54.7	81.7
3	$(DHQ)_2PYR$	22	76.2	87.9
4	$(DHQ)_2PYR$	0	80.7	80.0
5	$(DHQD)_2AQN$	22	63.5	97.4
6	$(DHQD)_2AQN$	0	66.6	81.7
7	$(DHQ)_2AQN$	22	26.9	90.1
8	$(DHQ)_2AQN$	0	23.7	64.7
9	$(DHQD)_2PHAL$	22	67.6	97.5
10	$(DHQ)_2PHAL$	22	27.2	70.1

The stereochemistry at the C-2 carbon of the generated glycerol moiety in the major products of the reactions in the presence of $(DHQD)_2PHAL$ and $(DHQ)_2PYR$ was then established. An optically pure diol **20** was obtained by selective-crystallization of the mixtures of diols **19** using di-isopropyl ether. The hydroxyl groups of the glycerol portion of the crystalline diol **20** were then benzylated in the usual manner to give compound **22**. Cleavage of **22** (2N HCl / dioxane, 50°C) furnished the dibenzyl glycerol derivative **23** and the anomeric mixture of benzylated fructopyranosides **24**. The products obtained (**23** and **24**) were purified by column chromatography. Comparison of the ^1H and ^{13}C-NMR spectra, and specific rotation values of **23**, with the values reported earlier for the pure dibenzyl glycerols [22,23] permitted assignment of the *R* configuration to the C-2 position of the optically pure diol [16] derived using $(DHQD)_2PHAL$ ligand. Based on this assignment, the optically pure diol derived by asymmetric dihydroxylation reaction carried out in the presence of the $(DHQ)_2PYR$ dihydroquinine ligand,

would have been expected to give the diol **21** with the *S* configuration at C-2 position. However, the specific rotation value for the dibenzyl glycerol derivative from the optically pure diol derived from $(DHQ)_2PYR$ ligand was the same in magnitude and sign for that observed for the product derived from compound **22**. These results suggest that the catalytic asymmetric dihydroxylation of the perbenzylated derivative **18** in the presence of $(DHQ)_2PYR$ and $(DHQD)_2PHAL$ ligands resulted in the generation of the same configuration of the diol (*R*-isomer), which was obtained as the major product.

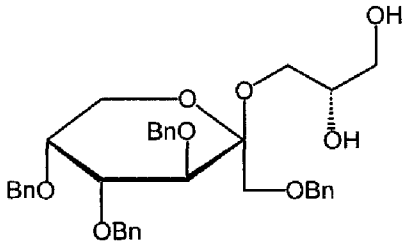


18



19

Previous results [16,18,26] indicate that it is not always possible to achieve respectable diastereoselectivity during osmylation of alkenyl glycosides in the presence of chiral auxiliaries. A number of factors play an important role. These include the length of the alkenyl chain, the position of unsaturation, the nature and size of the protecting functions, anomeric configuration, and the preferred conformation of the sugar rings involved. These intrinsic intramolecular factors seem to outweigh the other considerations which determine diastereofacial preferences in these chiral catalyzed dihydroxylation processes.



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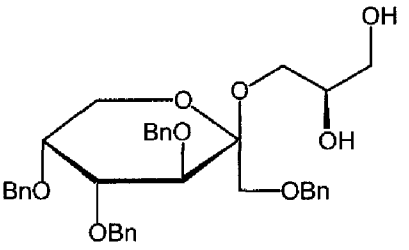
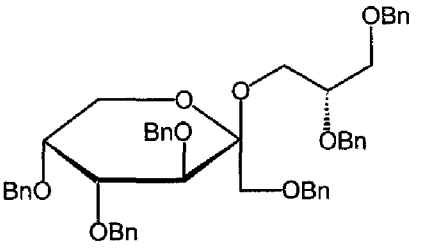
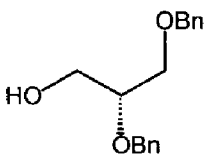


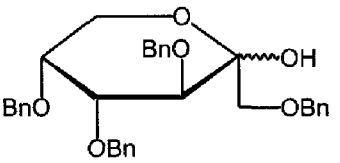
21



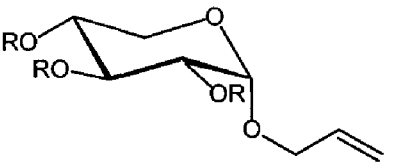
22



23



24



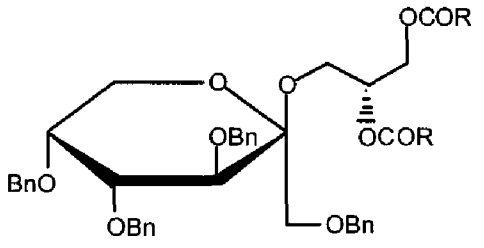
25 R = $C_6H_{11}CO$

3.2.2 Synthesis of some 2,3-di-*O*-acyl-1-*O*-(1',3',4',5'-tetra-*O*-benzyl β-D-fructopyranosyl)-*sn*-glycerol derivatives.

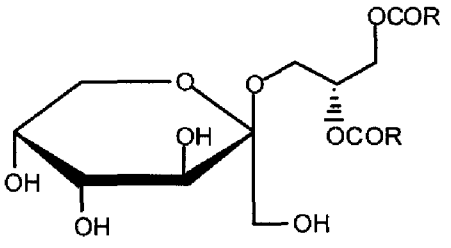
Natural glyceroglycolipids usually occur with the hydroxyl groups of the glycerol moiety esterified by a variety of saturated or unsaturated long chain fatty acids. The syntheses of these

compounds frequently involve the acylation of the hydroxyl groups of the protected glycosyl moieties, using fatty acids chlorides as acylating agents. These derivatives can also be prepared using the "orthoester" method which involves the catalytic condensation of 1,2-di-*O*-acyl-*sn*-glycerols with glycosyl orthoesters.[24] Several attempts have also been made to obtain these derivatives, having identical or different acyl groups on the glycerol moiety, starting from natural lipids.[25] Some syntheses of these compounds have been found to involve reactions of the glycerol portion with various activated long-chain carboxylic acids esters catalyzed by enzymes. Selective syntheses of monoester derivatives in reactions catalyzed by enzymes, using various acyl carriers with different chain length, have also been achieved (see Chapter 2 for details). The syntheses of these derivatives, carried out in the presence of enzymes, do in most cases not involve the protection of the carbohydrate portion. This is not the case for the chemical syntheses of these derivatives which require protection of the glycosyl moiety. Selective removal of blocking groups of the carbohydrate portion without affecting ester groups on the glycerol moiety can present problems, since many glycerol derivatives are formed using acetylated sugar derivatives (see chapter 2).

The synthesis of di-*O*-acyl esters of fructosyl glycerol derivatives has not yet been reported (see Chapter 1). The asymmetric dihydroxylation reaction (Sharpless type) of **18** which gives the optically active diol **20**, after selective crystallization, now permitted the synthesis of these derivatives.



26 R = $C_{11}H_{23}$ (91.3 %)
27 R = $C_{13}H_{27}$ (76.7 %)
28 R = $C_{15}H_{31}$ (83.3 %)



29 R = $C_{11}H_{23}$ (50 %)
30 R = $C_{13}H_{27}$ (57.9%)
31 R = $C_{15}H_{31}$ (53.9 %)

The preparation of these compounds could be easily effected by acylation of the two free hydroxyl groups of **20** using fatty acid chlorides. For the syntheses of compounds **26**, **27**, and **28**, a slight excess of fatty acid chloride (lauroyl, myristic, and palmitoyl) was required. Treatment of the diol **20** in pyridine with the fatty acid chloride in the usual manner gave the diester derivatives **26**, **27**, and **28**. The acylation of **20** with myristoyl and palmitoyl chlorides to furnish the respective diester derivatives **27** and **28**, was slower compared with the reaction of **20** with lauroyl chloride. The products obtained were purified by column chromatography (n-hexane-ethyl acetate, 3:1). The debenzylated derivatives were then obtained by catalytic hydrogenolysis (H_2, Pd/C) of **26**, **27**, and **28** in methanol to give the corresponding diester derivatives **29** (50%), **30** (57.9%), and **31** (53.9%). These new di-acyl glycolipids derivatives will be subjected to biological testing and appraisal of physical properties in due course.

3.3 Concluding remarks

Synthesis of 2, 3-dihydroxypropyl β-D-fructopyranoside (fructosyl glycerol) **20** from the allyl glycoside **9** has been successfully achieved using asymmetric dihydroxylation reactions (Sharpless type). The product **20** was obtained in an optically pure form by selective crystallisation. Degradation studies showed the material to possess the *R* configuration at the C-2 position of the glycerol unit. The use of benzyl groups as temporary protecting groups was important in this study. Some long-chain acyl ester derivatives as analogues of natural glyceroglycolipids were prepared by treatment of the intermediate diol **20** with long-chain carboxylic acid chlorides followed by removal of the benzyl ether protecting groups by catalytic hydrogenolysis.

3.4 Experimental section

The general conditions described here are applicable to all subsequent chapters.

General methods:

Optical rotations were determined with a Perkin-Elmer automatic polarimeter, model 241MC at 20°C on 1% solutions in the solvents indicated. Melting points were determined using a Reichert thermopan microscope equipped with crossed polarisers, and are uncorrected. Column chromatography was performed on silica gel 60 (Merk) with the eluents indicated. Thin-layer chromatography (TLC) on pre-coated plates of silica gel (Merk) was conducted in the solvent mixtures indicated. Detection was affected by spraying with 3% H_2SO_4 in ethanol and heating at 140°C. Spectral data for the compounds synthesized were obtained from ^{1}H-NMR spectra measured on a Bruker AC 100 (100 MHz, FT), AC 300 (300 MHz, FT), and (400 MHz, FT) and AM 400 spectrometers operating at room temperature in $CDCl_3$ or D_2O, with TMS (0 ppm) and HDO (4.72 ppm) respectively as internal standards, ^{13}C-NMR were recorded using Bruker AC 100 (100 MHz), AC 300 (300 MHz), AM 400 spectrometers operating at 25.00, 75.00 and 100.6 MHz respectively, $CDCl_3$ (77.00 ppm) or 1,4-dioxane (external, 67.8 ppm) were used as standards. Elemental analyses were obtained on a Carlo Erba instrument CHNS-EA 1108 element analyzer. Mass spectra were recorded using a double focusing VG 7070E spectrometer in the mode indicated, or a Varian Saturn 2 GC-MS ion-trap system. GLC was performed with a Hewlett-Packard 5890 gas chromatograph, a fused capillary column (25m) coated with HP-1 crossed-linked methyl silicone (gumphase) operating at 100-200°C (t = 0 min, isothermal, t = 5 min, 5°C min^{-1}) and nitrogen as the carrier gas at 2 mL.min^{-1} was used. All solvents were dried under standard conditions.

Allyl 1,3,4,5-tetra-O-*acetyl* β-D-*fructopyranoside (10)*

Compound **9** (5.02 g, 22.81 mmol) was acetylated in the usual manner with acetic anhydride (20 mL) and pyridine (35 mL) to give the known [7] tetra-acetate **10** as a syrup (8.61 g, 97.2%) after column chromatography (n-hexane-ethyl acetate, 3:1). $[\alpha]_D$ −127.5° ($CHCl_3$); Lit [7] $[\alpha]_D$ −127.5° ($CHCl_3$).

Allyl 1,3,4,5-tetra-O-*ethoxyethyl* β-D-*fructopyranoside (14)*

A cooled (15°C) stirred suspension of allyl β-D-fructopyranoside (**9**) (5g, 22.7 mmol) in 1,2-dimethoxyethane (50 mL) containing pyrimidium-*p*-toluenesulfonate (0.5 g) was treated

with ethylvinyl ether (17.4 mL, 0.182 mmol, 8 eq) . The reaction mixture was stirred until a clear solution was obtained (approximately 1 hr) and then at room temperature until a very slight yellowish colour had developed (approximately 5 hr, TLC, n-hexane-ethyl acetate, 3:1). A saturated aqueous solution of sodium hydrogen carbonate (50 mL) was added followed by ether (100 mL) and water (50 mL). The layers were separated, and the aqueous layer was washed with ether (50 mL). The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo*, and column chromatography (n-hexane-ethyl acetate, 3:1) of resultant crude material gave compound **14** (11.47 g, 98%).

2,3-Dihydroxypropyl 1',3',4',5'-tetra-O-ethoxyethyl-β-D-fructopyranoside (15)

(a) using $K_3Fe(CN)_6$ and $(DHQD)_2$.PHAL:-

A mixture of $(DHQD)_2$.PHAL (8.0 mg), $K_2OsO_2(OH)_4$ (1.6 mg), K_2CO_3 (415 mg), and $K_3Fe(CN)_6$ (980 mg) in water (5 mL) was added to a cooled (0 C) solution of **14** (508 mg, 1.0 mmol) in *tert.*-butyl alcohol (5 mL). The reaction mixture was stirred vigorously for 5 hr. The reaction was quenched by addition of Na_2SO_3 (1.5 g) and stirred for 1 hr. The reaction mixture was then diluted with water (10 mL) and extracted with ether (3x15 mL). The combined organic layers were washed with saturated aqueous solution of sodium chloride (10 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give **15** (535 mg, 98%) as a syrup.

A sample of compound **15** (102.9 mg, 0.20 mmol) in pyridine (5 mL) was acetylated with acetic anhydride in the usual manner. The resultant product was then treated with aqueous acetic acid (80%, 1 mL) at room temperature for 1 hr. Water (10 mL) was added and the solution lyophilized to give the deprotected product (58.2 mg) which was acetylated in the usual manner to give a quantitative yield of hexaacetylated product. $[\alpha]_D$ -110.5° ($CHCl_3$, c = 0.52 %), GLC : de = 51%.

(b) using $K_3Fe(CN)_6$ and $(DHQ)_2$.PHAL:-

Compound **14** (508 mg, 1.0 mmol) was converted in the same manner in the presence of $(DHQ)_2$.PHAL as a chiral ligand to furnish **15** (524 mg, 96%) as a syrup.

A sample of compound **15** (567 mg, 1.10 mmol) in pyridine (5 mL) was acetylated with acetic anhydride in the usual manner. The resultant product was then treated with aqueous acetic acid (80%, 1 mL) at room temperature for 1 hr. Water (10 mL) was added and the solution lyophilized to give the deprotected product (350 mg) which was acetylated in the usual manner to give a quantitative yield of hexaacetylated product. $[\alpha]_D$ -110.5° ($CHCl_3$, c = 0.52 %), GLC : de = 6%.

(c) using potassium permanganate:-

A solution of potassium permanganate (1.49 g, 9.45 mmol) in water (45 mL) was added dropwise to a stirred cooled (0°C) solution of **14** (4.57 g, 8.99 mmol) in acetone (45 mL) and water (23 mL). The reaction mixture was maintained at this temperature for 1 hr (TLC). The precipitated manganese dioxide was collected by filtration, washed successively with water (100 mL), acetone (50 mL), and ether (50 mL). The aqueous layer was extracted with ether (3x50 mL), and the combined ethereal extracts were washed with saturated aqueous solution of sodium chloride (100 mL), dried ($MgSO_4$), and concentrated *in vacuo* (4.78g, 98%).

A sample of compound **15** (205.9 mg, 0.40 mmol) in pyridine (5 mL) was acetylated with acetic anhydride in the usual manner. The resultant product was then treated with aqueous acetic

acid (80%, 1 mL) at room temperature for 1 hr. Water (10 mL) was added and the solution lyophilized to give the deprotected product (117 mg) which was acetylated in the usual manner to give a quantitative yield of hexaacetylated product. $[\alpha]_D$ -106.5° ($CHCl_3$, c = 0.52 %), GLC : de = 22%.

2,3-Dihydroxypropyl 1',3',4',5'-tetra-O-*acetyl* β-**D**-*fructopyranoside (16)*

A solution of potassium permanganate (3.43 g, 21.78 mmol) in water (90 mL) was added dropwise to a stirred, cooled (0°C) solution of **10** (8.05 g, 20.74 mmol) in acetone (90 mL) and water (46 mL). The reaction mixture was maintained at this temperature for 1 hr (TLC). The precipitated manganese dioxide was collected by filtration, washed successively with water (100 mL), acetone (50 mL), and ether (50 mL). The aqueous layer was extracted with ether (3x50 mL), and the combined ethereal extracts were washed with brine (100 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give **16** (4.80 g, 54.6%) as a colourless oil. A sample of **16** was crystallized from di-isopropyl ether / ethyl acetate; m.p 120-125 C; $[\alpha]_D$ –113° ($CHCl_3$). ^{13}C-NMR (100 MHz, $CDCl_3$): δ, 170.5, 170.4, 170.2, 170.1, 169.6, 96.8, 96.7, 70.5, 70.2, 68,9, 68.8, 68.4, 67.9, 67.7, 64.0, 63.8, 63.3, 62.8, 62.0, 21.0, 20.7. *Anal.* calc. for $C_{17}H_{26}O_{12}$: C, 48.34; H, 6.20. Found: C, 48.51; H,6.25.

A sample of compound **16** (38.8 mg, 0.091 mmol) in pyridine (5 mL) was acetylated with acetic anhydride in the usual manner to give a quantitative yield of hexaacetylated product. $[\alpha]_D$ -109° ($CHCl_3$), GLC : d.e = 50%.

2,3-Bis-O-p-*nitrobenzoylpropyl 1',3',4',5'-tetra*-O-*acetyl* β-**D**-*fructopyranoside (17)*

A cooled (0°C), stirred solution of compound **16** (241 mg, 0.571 mmol) in pyridine (10 mL) was treated with *p*-nitrobenzoylchloride (288 mg, 1.55 mmol) and then set aside at room temperature for 48 hr. The resultant solid material was filtered, washed with water and dried. A solution of the material in DMF (6 mL) was poured into ice-water (50 mL) and the resultant solid material was collected by filtration, washed with ice-cold water, and dried *in vacuo* (P_4O_{10}) to give an armophous material (316 mg, 77%). $[\alpha]_D$ –103.1° ($CHCl_3$). *Anal.* calc. for $C_{31}H_{32}O_{18}N_2$: C 51.67; H, 4.48; N, 3.89. Found: C, 51.53; H, 4.35; N, 3.92 %.

Allyl 1,3,4,5-tetra-O-*benzyl* β-**D**-*fructopyranoside (18)*

A cooled (0°C) stirred mixture of allyl β-**D**-fructopyranoside (**9**) (7.4139 g, 33.7 mmol) in dimethyl sulfoxide (30 mL) containing powdered potassium hydroxide (7.54 g, 134.8 mmol, 4 eq) was treated with benzyl chloride (15.5 mL, 134.8 mmol, 4 eq). The mixture was stirred at room temperature for *ca* 12 hr and then treated with ether (100 mL) and water (40 mL). The separated aqueous layer was extracted with ether (50 mL), and the combined organic layers were washed with saturated sodium chloride (3x20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Column chromatography (n-hexane-ethyl acetate, 3:1) of the crude material gave compound **18** (15.5 g, 79.3%) as a pure colourless oil. $[\alpha]_D$ –49.6° ($CHCl_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 138.84, 138.62, 138.47, 137.99, 128.20, 128.07, 128.02, 127.67, 127.57, 127.37, 127.22 (aromatic-C), 135.12 (-OCH_2CH=CH_2), 115.88 (-OCH_2CH=CH_2), 101.83 (C-2), 78.73 (C-3), 76.17 (C-4), 75.43 (benzylic-C), 73.62 (C-5), 73.43, 72.17, 71.09 (benzylic-C), 70.15 (C-1), 62.20 (C-1'), and 61.14 (C-6) ppm. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.40-7.19 (m, 20H, aromatic H), 5.93-5.84 (m, 1H, H-2'), 5.23 (dd, 1H, $J_{2,3'a}$ =15.8 Hz, $J_{3'a,3'b}$ = 1.3 Hz H-3'a), 5.0 (dd, 1H, $J_{2,3'b}$ = 11.0 Hz, $J_{3'a,3'b}$ = 1.3 Hz H-3'b), 4.93, 4.62 (2d, 2H, J =11.2 Hz, benzylic-H), 4.76, 4.71

(2d, 2H, J = 12.6 Hz, benzylic-H), 4.68, 4.45 (2d, 2H, J = 11.9 Hz, benzylic-H), 4.39 (d, 1H, H-3), 4.12-4.14 (m, 2H, H-1'a, H-1'b), 4.10 (m, 1H, H-5), 4.01 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.1 Hz, H-4), 3.87 (dd, 1H, $J_{5,6eq}$=1.4 Hz, $J_{6ax,6eq}$ = -12.4 Hz, H-6eq), 3.84 (2d, 1H, J = -10.1 Hz, H-1a), 3.77 (2d, 1H, J= -10.1 Hz, H-1b), 3.55 (dd, 1H, $J_{5,6ax}$ = 1.4 Hz, $J_{6ax,6eq}$=-12.4Hz, H-6ax) ppm.

*2(**R**),3-Dihydroxypropyl 1',3',4',5'-tetra-*O*-benzyl-β-**D**-fructopyranoside (**20**)*
*[1-O-(1',3',4',5'-tetra-*O*-benzyl β-**D**-fructopyranosyl)-**sn**-glycerol]*

A mixture of $(DHQD)_2$.PHAL (136.1 mg), $K_2OsO_2(OH)_4$ (24.43 mg), K_2CO_3 (7.33 g), and $K_3Fe(CN)_6$ (17.28 g) in water (50 mL) was added to a stirred solution of **17** (10.121 g, 17.45 mmol) in *tert*-butyl alcohol (50 mL). The reaction mixture was then stirred vigorously at room temperature for *ca* 12 hr. The reaction mixture was quenched by addition of Na_2SO_3 (30 g), stirred for 1 hr and then diluted with ether (100 mL) and water (60 mL). The aqueous layer was washed with ether (2x50 mL) and the combined organic layers were washed with saturated sodium chloride (40 mL), dried (MgSO4), and concentrated *in vacuo*. Column chromatography (n-hexane-ethyl acetate, 1:3) of the crude material gave compound **19** (9.697 g, 90.5%) as white crystals. Crystallization of **19** from di-isopropyl ether yielded pure compound **20** (6.5 g, 60%). m.p. 101-102°C; $[\alpha]_D$ –59.3° ($CHCl_3$); MS (CI-CH_4) M/z 615 (M^++H^+), 523 (M^++H^+-$OHCH_2CH(OH)CH_2OH$). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 138.34, 138.27, 137.66, 128.21, 128.12, 128.03, 127.77, 127.63, 127.53, 127.43 (aromatic-C), 101.04 (C-2), 78.58 (C-3), 76.49 (C-4), 75.60, 73.53 (benzylic-C), 73.24 (C-5), 71.94, 71.12 (benzylic-C), 70.09 (C-2', C-3'), 63.69 (C-1', C-1), and 61.03 (C-6) ppm. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.39-7.17 (m, 20H, aromatic H), 4.87, 4.61 (2d, 2H, J = 10.8 Hz, benzylic-H), 4.73, 4.69 (2d, 2H, J = 12.6 Hz, benzylic-H), 4.58, 4.42 (2d, 2H, J = 11.9 Hz, benzylic-H), 4.33 (d, 1H, J = 10.0 Hz, H-3), 3.90 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.0 Hz, H-4), 3.85 (dd, 1H, $J_{5,6eq}$ = 1.8 Hz, $J_{6ax,6eq}$ = -12.4 Hz, H-6eq), 3.55 (dd, 1H, $J_{5,6ax}$ = 1.7 Hz, $J_{6ax,6eq}$ = -12.4 Hz, H-6ax), 3.73 (2d, 1H, J = -10.2 Hz, H-1a), 3.72 (m, 1H, H-5), 3.61 (2d, 1H, J = -10.2 Hz, H-1b), 3.52 (m, 1H, H-2'), 3.44-3.41 (m, 2H, H-1'b, H-1'a), 3.35 (dd, 1H, J = 6.1 Hz, H-1'b), 3.42 (d, 1H, $J_{3'a,2}$ = 6.1 Hz, H-3'a), 3.39 (d, 1H, $J_{3'b,2}$ = 6.1 Hz, H-3'b), 2.97 (bs, 1H, O*H*), 2.26 (bs, 1H, O*H*) ppm. *Anal* calc for $C_{37}H_{42}O_8$: C 72.29; H 6.89. Found: C 72.45; H 6.87%.

In another experiment a stirred, cooled (0°C) solution of **17** (5.06 g, 8.725 mmol) in *tert*-butyl alcohol (50 mL) and water (50 mL) was treated with a mixture of $(DHQD)_2$.PYR (68.05 mg), $K_2OsO_2(OH)_4$ (12.22 mg), K_2CO_3 (3.67 g) and $K_3Fe(CN)_6$ (8.64 g), set aside at 0°C for 12 h. and processed as described above to give pure compound **20** (2.708 g, 50%). m.p. 101-103°C (diisopropyl ether). $[\alpha]_D$ –59° ($CHCl_3$). The spectral characteristics were identical to those reported and the compound was identical, in all respects, with **20** obtained as described (*vide supra*).

*2(**R**)-Dibenzoxypropyl 1',3',4',5'-tetra-*O*-benzyl-β-**D**-fructopyranoside (**22**)*

A solution of compound **20** (1.603 g, 2.6 mmol) in dimethyl sulfoxide (10 mL) containing powdered potassium hydroxide (436.8 mg, 7.8 mmol, 3 eq) was benzylated in the usual manner using benzyl chloride (0.8 mL, 7.8 mmol, 3 eq). Column chromatography (n-hexane - ethyl acetate, 3:1) of the crude material gave compound **22** (1.828 g, 77%) as a pure colourless oil. $[\alpha]_D$ –57.4° ($CHCl_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 138.50, 138.35, 138.34, 137.71, 128.29, 128.17, 127.85, 127.86, 127.79, 127.68, 127.65, 127.57, 127.53 (aromatic-C), 100.95 (C-2), 78.73 (C-3), 76.65 (C-4), 75.52, 73.66 (benzylic-C), 70.24 (C-1'), 68.50 (C-3'),

64.85 (C-1), 61.24 (C-6), 19.55 (CH_3).ppm. ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 7.44-7.21 (m, 30H, aromatic-H), 4.98, 4.61 (d, 1H, J = 11.4 Hz, benzylic-H), 4.77, 4,71 (2d, 2H, J = 12.8 Hz, benzylic -H), 4.68-4.57 (m, 8H, benzylic-H), 4.44 (1d, 1H,J = 11.9 Hz, benzylic-H), 4.36 (d, 1H, J = 10.1 Hz, H-3), 3.96, 3.90 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.2 Hz, H-4), 3.85-3.54 (m, 9H, H-1a, H-1b, H-1'a, H-1'b, H-2', H-3', H-5, H-6eq, H-6ax), 1.17 (d, 3H,CH_3) ppm.

*2(**R**)-Di-O-benzylpropanetriol (23)*

Compound **22** (984 mg) was treated with a mixture of trifluoroacetic acid / water = 9 : 1 (5 mL) at room temperature for 10 mins. The resultant mixture was diluted with ether (100 mL) and the separated organic layer washed sequentially with ice cold brine (2 x 20 mL) and saturated aqueous sodium hydrogen carbonate (10 mL), dried ($NaSO_4$), concentrated *in vacuo* and purified by column chromatography (n-hexane - ethyl acetate, 9:1) to give compound **23** (129 mg, 36%) as a colourless oil. $[\alpha]_D$ +17.0° ($CHCl_3$); lit [23] $[\alpha]_D$ +15.7° ($CHCl_3$); lit [22] $[\alpha]_D$ (enantiomer) −17.2° ($CHCl_3$). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 137.61, 128.47, 127.94, 127.69 (aromatic-C), 72.35, 70.20 (benzylic-C), 78.12, 65.13, 62.65 (glycerol C-1, C-2, C-3) ppm. ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 7.36-7.24 (m, 10H, aromatic-H), 4.66-4.53 (2s, each 2H, benzylic-H), 3.87-3.54 (m, 5H, aliphatic-H), 2.26 (bs, 1H, OH) ppm.

Further elution (CH_2Cl_2 - MeOH, 200:1) gave compound **24** (an anomeric mixture) as a colourless oil (511 mg, 61%). $[\alpha]_D$ −32° ($CHCl_3$). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 138.35, 138.08, 137.72, 137.63, 128.48, 128.38, 128.36, 128.33, 128.30, 128.14, 128.09, 127.99, 127.93, 127.85, 127.77, 127.70, 127.66, 127.58 (aromatic-C), 98.06 (β-anomer C-2), 97.38 (α-anomer C-2), 78.87, 75.73, 75.43, 74.41, 74.32, 73.98, 73.78, 73.72, 73.41, 73.16, 72.03, 71.97, 71.62, 71.41, 71.18 (benzylic C and C-3 - C-5), 60.80 (2x, C-1α,β), 57.28 (2x C-6). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.41-7.10 (m, 32H, aromatic-H), 4.96-4.92 (d, 1H, benzylic-H), 4.80-4.76 (m, 1H, benzylic-H), 4.73-4.67 (m, 2H, benzylic-H), 4.63 (s, 2H, benzylic-H), 4.59-4.35 (m, 6H, benzylic -H), 4.06-3.95 (m, 2H), 3.93-3.64 (m, 6H, H-3, H-4), 3.55, 3.43 (dd, 2H, J_1 = 23.36 Hz, J_2 = 9.94 Hz, H-1 or H-6), 3.37 (d, 1H, J = 9.73 Hz, H-1 or H-6), 1.65 (bs, 1H, OH) ppm.

*2(**R**),3-Di-decanoxypropyl 1',3',4',5'-tetra-O-benzyl-β-**D**-fructopyranoside (26)*
*[1-O-(1',3',4',5'-tetra-O-benzyl β-**D**-fructopyranosyl)-**sn**-glycerol 2,3-di-dodecanoate]*

A stirred, cooled (0°C) solution of **20** (345 mg, 0.561 mmol) in dry pyridine (5 mL) was treated with a solution of dodecanoyl chloride (0.38 mL, 1.68 mmol, 3 eq) in dichloromethane (10 mL) and then maintained at room temperature for 2 hr. The mixture was treated with ice water, diluted with more dichloromethane (20 mL) and the combined organic layer was washed successively with aqueous hydrochloric acid (2**M**, 20 mL), water (20 mL), sodium hydrogen carbonate (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (n-hexane-ethyl acetate, 9:1) of the residue gave **26** (501 mg, 91.3%) as a pure colourless oil $[\alpha]_D$ −35.1° ($CHCl_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 173.3, 172.93 (*C*=O), 139.02, 138.52, 138.43, 137.86, 128.22, 128.03, 127.67, 127.51, 127.41, 127.11 (aromatic-C), 101.65 (C-2), 78.44 (C-3), 76.99 (C-4), 74.96, 73.68 (benzylic-C), 73.54(C-5), 72.28, 71.23 (benzylic-C), 70.00(C-1), 69.92 (C-2'), 62.44 (C-1'), 61.31 (C-6), 59.86 (C-3'), 34.21 ($COCH_2$), 34.06 ($COCH_2$), 31.86-22.64 (aliphatic C), and 14.08 (CH_3) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.40-7.19 (m, 20H, aromatic H), 5.21 (m, 1H, H-2'), 4.92, 4.62 (2d, 2H, J = 11.4 Hz, benzylic-H), 4.77, 4.71 (2d, 2H, J = 12.7 Hz, benzylic-H), 4.64, 4.43(2d, 2H, J = 11.9 Hz, benzylic-H), 4.60, 4.58 (2d, 2H, J = 11.6 Hz, benzylic-H), 4.32 (d, 1H, J = 10.0 Hz, H-3), 4.1 (dd, 1H, J = 6.2 Hz, H-1a'), 4.0 (dd,

1H, J = 6.2 Hz, H-1b'), 3.95, 3.91 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.1 Hz, H-4), 3.88 (dd, 1H, $J_{5,6eq}$ = 1.6 Hz, $J_{6ax,6eq}$ = -12.3 Hz, H-6eq), 3.84 (dd, 1H, $J_{5,6ax}$ = 1.5 Hz, $J_{6ax,6eq}$ = -12.3 Hz, H-6ax), 3.77 (m, 1H, H-5), 3.75 (2d, 1H, J = -10.2 Hz, H-1a), 3.62 (2d, 1H, J = -10.2 Hz, H-1b), 3.64 (dd, 1H, $J_{3'a,2'}$ = 6.5 Hz, H-3'a), 3.58 (dd, 1H, $J_{3'b,2'}$ = 6.5 Hz, H-3'b), 2.3-2.2 (m, 4H, $COCH_2$), 1.60-1.54 (m, 4H, $CH_2CH_2CH_3$), 1.25 (m, 32H, aliphatic H), and 0.87 (2xt, 6H, $2xCH_3$) ppm.

*2(**R**),3-Di-tetradecanoxypropyl 1',3',4',5'-tetra-*O*-benzyl-β-**D**-fructopyranoside (27)*
*[1-O-(1',3',4',5'-tetra-O-benzyl-β-**D**-fructopyranosyl)-**sn**-glycerol 2,3-di-tetradecanoate]*

Compound **20** (205 mg, 0.333 mmol) was treated with tetradecanoyl chloride (0.22 mL, 0.999 mmol, 3 eq) using the above procedure, for 4 hr. to yield compound **27**. Column chromatography (n-hexane - ethyl acetate, 9:1) of the crude material gave pure **27** (257 mg, 74.6%) as a colourless oil. $[\alpha]_D$ –28.0° ($CHCl_3$) ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 173.35, 172.96 (*C*=O), 139.07, 138.57, 138.49, 137.91, 128.26, 128.07, 127.74, 127.69, 127.55, 127.50, 127.45, 127.15 (aromatic-C), 101.69 (C-2), 78.49 (C-3), 76.58 (C-4), 74.99, 73.77 (benzylic-C), 73.59 (C-5), 72.33, 71.29 (benzylic-C), 70.13 (C-1), 69.97 (C-2'), 62.49 (C-1'), 61.37 (C-6), 59.92 (C-3'), 34.25, 34.10 ($COCH_2$), 31.89-22.70 (aliphatic C), and 14.10 (CH_3) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.53-7.19 (m, 20H, aromatic H), 5.21 (m, 1H, H-2'), 4.91, 4.61 (2d, 2H, J = 11.5 Hz, benzylic-H), 4.76, 4.73 (2d, 2H, J = 12.7 Hz, benzylic-H), 4.64, 4.43 (2d, 2H, J = 11.9 Hz, benzylic-H), 4.60, 4.58 (2d, 2H, J = 11.6 Hz, benzylic-H), 4.30 (d, 1H, J = 10.0 Hz, H-3), 4.1 (dd, 1H, 6.2 Hz, 1a'), 4.0 (dd, 1H, 6.2 Hz, H-1b'), 3.94, 3.90 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.1 Hz, H-4), 3.88 (dd, 1H, $J_{5,6eq}$ = 1.7 Hz, $J_{6ax,6eq}$ = -12.3 Hz, H-6eq), 3.84 (dd, 1H, $J_{5,6ax}$ = 1.6 Hz, $J_{6ax,6eq}$=-12.3 Hz, H-6ax), 3.77 (m, 1H, H-5), 3.75 (2d, 1H, J = -10.2 Hz, H-1a), 3.62 (2d, 1H, J = -10.2 Hz, H-1b), 3.64 (dd, 1H, $J_{3'a,2'}$ = 6.5 Hz, H-3'a), 3.58 (dd, 1H, $J_{3'b,2'}$ = 6.5 Hz, H-3'b), 2.3-2.2 (m, 4H, $COCH_2$), 1.62-1.53(m, 4H, $CH_2CH_2CH_3$), 1.25 (m, 40H, aliphatic H), and 0.87 (2xt, 6H, $2xCH_3$) ppm.

*2(**R**),3-Di-hexadecanoxypropyl 1',3',4',5'-tetra-O-benzyl-β-**D**-fructopyranoside (28)*
*[1-O-(1',3',4',5'-tetra-O-benzyl β-**D**-fructopyranosyl)-**sn**-glycerol 2,3-di-hexadecanoate]*

Treatment of **20** (182 mg, 0.296 mmol) with hexadecanoyl chloride (0.20 mL, 0.888 mmol, 3 eq) as above, followed by column chromatography (n-hexane - ethyl acetate, 9:1) gave compound **28** (255 mg, 79.0%) as a pure colourless oil $[\alpha]_D$ –33.2° ($CHCl_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 173.32, 172.95 (*C*=O), 139.07, 138.57, 138.48, 137.90, 128.25, 128.06, 127.73, 127.69, 127.54, 127.49, 127.44, 127.14 (aromatic-C), 101.69 (C-2), 78.48 (C-3), 76.57 (C-4), 74.98, 73.77 (benzylic-C), 73.58 (C-5), 72.32, 71.29 (benzylic-C), 70.12 (C-1), 69.96 (C-2'), 62.48 (C-1'), 61.37 (C-6), 59.91 (C-3'), 34.24, 34.10 ($COCH_2$), 31.90-22.68 (aliphatic C), and 14.10 (CH_3) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.40-7.21 (m, 20H, aromatic H), 5.28 (m, 1H, H-2'), 4.91, 4.61 (2d, 2H, J = 11.5 Hz, benzylic-H), 4.76, 4.73 (2d, 2H, J = 12.7 Hz, benzylic-H), 4.64, 4.43 (2d, 2H, J = 11.9 Hz, benzylic-H), 4.60, 4.58 (2d, 2H, J = 11.6 Hz, benzylic-H), 4.31 (d, 1H, J = 10.0 Hz, H-3), 4.1 (dd, 1H, 6.2 Hz, H-1a'), 4.0 (dd, 1H, 6.2 Hz, H-1b'), 3.94, 3.91 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.1 Hz, H-4), 3.87 (dd, 1H, $J_{5,6eq}$ = 1.7 Hz, $J_{6ax,6eq}$=-12.3 Hz, H-6eq), 3.83 (dd, 1H, $J_{5,6ax}$ = 1.6 Hz, $J_{6ax,6eq}$=-12.3 Hz, H-6ax), 3.77 (m, 1H, H-5), 3.75 (2d, 1H, J = -10.2 Hz, H-1a), 3.62 (2d, 1H, J = -10.2 Hz, H-1b), 3.64 (dd, 1H, $J_{3'a,2'}$ = 6.5 Hz, H-3'a), 3.58 (dd, 1H, $J_{3'b,2'}$ = 6.5 Hz, H-3'b), 2.3-2.2 (m, 4H, $COCH_2$), 1.60-1.53 (m, 4H, $CH_2CH_2CH_3$), 1.25 (m, 48H, aliphatic H), and 0.87 (2xt, 6H, $2xCH_3$) ppm.

*2(**R**),3-Di-decanoxypropyl-β-**D**-fructopyranoside (**29**)*
*[1-O-(β-**D**-fructopyranosyl)-**sn**-glycerol 2,3-di-dodecanoate]*

A solution of compound **26** (253 mg, 0.258 mmol) in methanol (30 mL) was subjected to hydrogenolysis in the presence of palladium on charcoal (10%, 60 mg) at room temperature for 2 hr. The catalyst was removed by filtration, washed with methanol and the combined filtrate and washings concentrated *in vacuo* to yield compound **29** as white crystals (83.6 mg, 50%). A sample of the product was crystallized (ether / ethanol) to give a pure **29**. m.p. 110-112°C; $[\alpha]_D$ –48.0° (DMF); MS (FAB-Na^+) M/z 641 (M^++ Na^+), 458 (M^++ Na^+–$COC_{11}H_{23}$), 257 (M^++ Na^+–2x$COC_{11}H_{23}$, –H_2O). ^{13}C-NMR [$CDCl_3$ + CD_3OD, 75 MHz] δ 173.79, 173.25 (*C*=O), 100.12 (C-2), 70.20 (C-3), 70.03 (C-4), 69.95 (C-5), 69.11 (C-2'), 63.64 (C-1), 62.43 (C-6), 62.29 (C-1'), 59.54 (C-3'), 34.12, 33.96 (-CO*C*H_2), 31.73-22.49 (aliphatic C) and 13.87 (*C*H_3) ppm. ^{1}H-NMR [$CDCl_3$ + CD_3OD, 400 MHz] δ 5.20 (m, 1H, H-2'), 4.40, 4.38 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.6 Hz, H-4), 4.18 (dd, 1H, 6.6 Hz, H-1a'), 4.16 (dd, 1H, 6.6 Hz, H-1b'), 3.90 (d, 1H, J = 9.8 Hz, H-3), 3.80-3.68 (m, 7H, H-1, H-3', H-5, H-6), 2.3-2.2 (m, 4H, CO*C*H_2), 1.58 (m, 4H, CH_2C*H*$_2CH_3$), 1.26 (m, 32H, aliphatic H), and 0.87 (2xt, 6H, 2x*C*H_3) ppm. *Anal* calc for $C_{33}H_{62}O_{10}$: C 64.05; H 10.10. Found: C 64.40; H 9.83%.

*2(**R**),3-Di-tetradecanoxypropyl-β-**D**-fructopyranoside (**30**)*
*[1-O-(β-**D**-fructopyranosyl)-**sn**-glycerol 2(**R**),3-di-tetradecanoate]*

Compound **27** (836 mg, 0.808 mmol) in methanol (30 mL) was subjected to hydrogenolysis as above to give compound **30** (316 mg, 57.9%) as white crystals (ether - ethanol). m.p. 116°C; $[\alpha]_D$ –45.4° (DMF); MS (FAB-Na^+) M/z 697 (M^++ Na^+), 514 (M^++ Na^+–$C_{13}H_{27}$), 285 (M^++ Na^+–$C_{13}H_{27}$, –$COC_{13}H_{27}$, –H_2O). ^{13}C-NMR [$CDCl_3$ + CD_3OD, 75 MHz] δ 173.69, 173.15 (*C*=O), 100.11 (C-2), 70.19 (C-3), 70.13 (C-4), 69.98 (C-5), 69.11 (C-2'), 63.62 (C-1), 62.39 (C-6), 62.25 (C-1'), 59.52 (C-3'), 34.12, 33.90 (-CO*C*H_2), 31.73-22.49 (aliphatic C) and 13.87 (*C*H_3) ppm. ^{1}H-NMR [$CDCl_3$ + CD_3OD, 400 MHz] δ 5.22 (m, 1H, H-2'), 4.41, 4.39 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.6Hz, H-4), 4.20 (dd, 1H, J = 6.6 Hz, H-1a'), 4.18 (dd, 1H, J = 6.6 Hz, H-1b'), 3.92 (d, 1H, J = 9.8 Hz, H-3), 3.80-3.68 (m, 7H, H-1, H-3', H-5, H-6), 2.3-2.2 (m, 4H, CO*C*H_2), 1.58 (m, 4H, CH_2C*H*$_2CH_3$), 1.26 (m, 40H, aliphatic H), and 0.87 (2xt, 6H, 2x*C*H_3) ppm. *Anal* calc for $C_{37}H_{70}O_{10}$: C 65.84; H 10.45. Found: C 65.87; H 10.57%.

*2(**R**),3-Di-hexadecanoxypropyl-β-**D**-fructopyranoside (**31**)*
*[1-O-(β-**D**-fructopyranosyl)-**sn**-glycerol 2,3-di-hexadecanoate]*

Hydrogenolysis of compound **28** (200 mg, 0.183 mmol) in methanol (30 mL) gave compound **31** (62.24 mg, 53.9%) as white crystals (ether - ethanol). m.p. 120°C; $[\alpha]_D$ –44.4° (DMF); MS (FAB-Na^+) M/z 752 (M^++ Na^+), 330 (M^++ Na^+–2x$C_{15}H_{31}$), 312 (M^++ Na^+–$C_{15}H_{31}$, –$C_{15}H_{31}$, –H_2O). ^{13}C-NMR [$CDCl_3$ + CD_3OD, 75 MHz] δ 173.76, 173.34 (*C*=O), 100.13 (C-2), 70.18 (C-3), 70.12 (C-4), 69.97 (C-5), 69.11 (C-2'), 63.63 (C-1), 62.38 (C-6), 62.24 (C-1'), 59.53 (C-3'), 34.12, 33.90 (-CO*C*H_2), 31.73-22.49 (aliphatic C) and 13.87 (*C*H_3) ppm. ^{1}H-NMR [$CDCl_3$ + CD_3OD, 400 MHz] δ 5.23 (m, 1H, H-2'), 4.42, 4.40 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.6 Hz, H-4), 4.22 (dd, 1H, J = 6.6 Hz, H-1a'), 4.19 (dd, 1H, J = 6.6 Hz, H-1b'), 3.94 (d, 1H, J = 9.8 Hz, H-3), 3.80-3.68 (m, 7H, H-1, H-3', H-5, H-6), 2.3-2.2 (m, 4H, CO*C*H_2), 1.58 (m, 4H, CH_2C*H*$_2CH_3$), 1.26 (m, 48H, aliphatic H), and 0.87 (2xt, 6H, 2x*C*H_3) ppm. *Anal* calc for $C_{39}H_{74}O_{10}$: C 65.86; H 10.44. Found: C 65.89; H 10.54%.

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CHAPTER 4

SYNTHESIS AND REACTIONS OF SOME SPIRO-FRUCTOSIDES AND QUASI-DISACCHARIDES FROM ALLYL β-D-FRUCTOPYRANOSIDE [#]

4.1 Introduction

During structural studies on some glycerol derivatives of D-fructose compounds **1** and **2** (see Chapter 3) were subjected to periodate oxidation. Appropriate removal of the protecting functions from the products gave in each case the same crystalline compound. The ^{1}H-NMR spectrum of the material, presumed to be the glycolaldehyde (hydroxyacetaldehyde) fructoside **3**, did not contain signals expected for an aldehyde function at 9-10 ppm. Previous studies on glycosides of this type have suggested that they exist in the free aldehyde form [1] (but with no supportive evidence), or as the intramolecular cyclic hemiacetals.[2] This particular study described a number of lipophilic derivatives obtained by reductive ozonolysis of allyl glycosides. The products were shown by ^{1}H-NMR spectroscopy to be cyclic hemiacetals involving the C-2 hydroxyl group of the parent carbohydrate ring. It seemed likely that the product obtained during this study was the *spiro* hemiacetal **4** [(3,6*S*,9*R*,10*R*,11*S*)-1,4,7-trioxaspiro[5,5]undecane-3,9,10,11-tetrol]. This would have resulted from the *in situ* cyclisation of the produced aldehyde group with the primary C-1 hydroxyl function of the fructopyranoside ring, although the alternative structure **5** involving C-3 OH could not be precluded. Little is known of the fundamental properties of spiroacetals of this type which possess the equivalent of an anomeric reducing centre at C-3 of the spiroundecane system. The synthesis and some reactions of the bicyclic triol **6** have been reported [3] but this compound lacks a reactive group at C-3. Many important natural products also have spiroacetal linkages in their structures.[4] These include insect pheromones, antiparasitic agents and polyether antibiotics. It was decided to investigate some basic characteristic carbohydrate-type reactions of compound **4** in order to produce some "quasi" saccharide derivatives as potential carbohydrate mimics. There is considerable current interest in the glycobiology of saccharide mimics, especially those in which the interglycosidic linkages have been replaced by methylene groups.[5] The results of this study are presented in this chapter.

[#]The term "quasi" is employed because others [6] have used the alternative term "pseudo" to describe unusual oligosaccharides.

[#]A major portion of this work has been reported, see, "Synthesis and reactions of some derivatives of (3,6*S*,9*R*,11*S*)-1,4,7-trioxaspiro[5,5]undecane-3,9,10,11-tetrol: novel quasi-saccharides." Regeling, H., Sung'hwa, F., Zwanenburg, B., de Gelder, R., and Chittenden, G. J. F. *Carbohydr. Polymers.* **1998**, *37*, 323-333.

4.2 Results and discussion

Reductive ozonolysis (O_3-Ph_3P) of the previously described [7] allyl β-D-fructopyranoside (**7**) also produced compound **4** in excellent yield (87.5%) and it was decided to use this procedure for its production rather than starting from compounds **1** and **2**. The product, a mixture of isomers, was acetylated (acetic anhydride-pyridine) in the usual manner to give a mixture of the two "anomeric" peracetates **8** and **9** in a 1:2 ratio. A portion of the material was separated by column chromatography. In keeping with simple carbohydrate convention compound **8** was assigned the α configuration, in which the C-3 acetoxy group (3*R*) assumes an axial disposition. Compound **9**, likewise, was the C-3 (*S*) acetoxy derivative with an equatorial (β) disposition. These assignments were confirmed by X-ray structural analyses on compounds **8** and **9** (see figs 1 and 2, see appendix for supplementary data). Acetylation of **4** using acetic anhydride-sodium acetate gave a mixture of **8** and **9** in a 1:3 ratio (GLC), which was not separated. Treatment of compound **4** with *p*-nitroaniline in the conventional manner [8] gave the crystalline *p*-nitrophenyl-amino derivative **10** which had an unusually high positive specific rotation of $[\alpha]_D$ +281° for a derivative of β-D-fructopyranose. It was assigned the α-configuration on the basis of this value and by supportive ^{1}H-NMR data. The signals for the C-3 proton coupling with the NH group appeared as a doublet-doublet at δ 5.03 ppm in DMSO-D_6. This reduced to an approximate broad doublet when the spectrum was recorded in DMSO-D_6 - D_2O, as a result of partial exchange with the NH group. It is well known that glycosylamines can anomerise under these conditions. Compound **10** was characterized by acetylation (pyridine - acetic anhydride) in the usual manner to give the tri-*O*-acetate **11**.

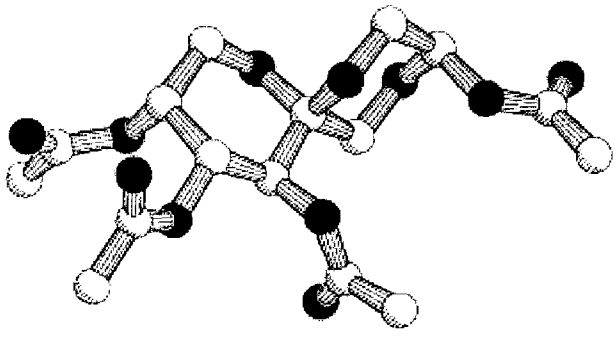


Figure 1: PLUTON drawing of compound **8**

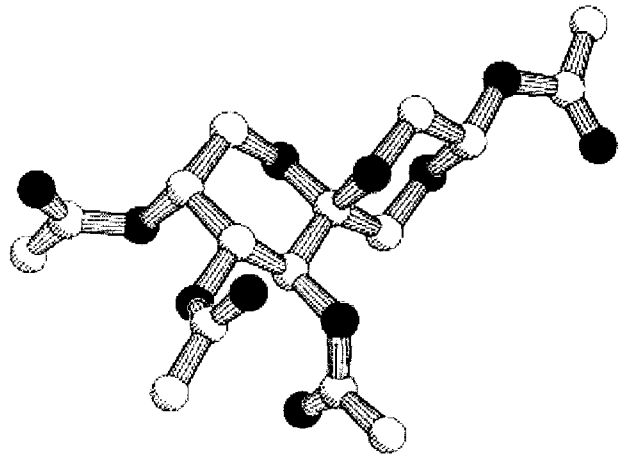
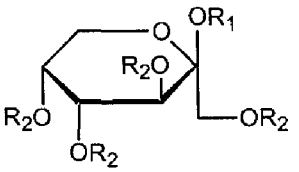


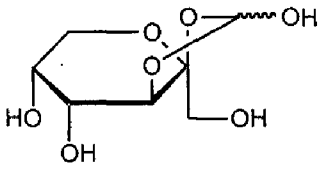
Figure 2: PLUTON drawing of compound **9**

Treatment of a mixture of compounds **8** and **9** with a 33% solution of hydrogen bromide in glacial acetic acid gave the bromide **12** as a syrup (94%). It is noteworthy that **12** was not stable when stored as a syrup, but could be kept for considerable periods (*ca* 3 months) in dichloromethane solution at 0°C without deterioration. The putatively assigned 3*R* (α) configuration of this derivative was based on the known characteristics of the precursors **8** and **9**, (X-ray structures), the expected preferred axial disposition of the 3-bromo group, the

comparatively low negative rotational value ($[\alpha]_D$ = -40°) and on its ^{1}H-NMR spectrum. Treatment of **12** with excess of methanol in the presence of anhydrous sodium carbonate for 30 minutes, followed by column chromatography (hexane - ethylacetate, 1:1), yielded two crystalline products. The first of these was the "β" glycoside **13** obtained in 49% yield, which was followed by the α-anomer **14** (21%). It was of interest that **13** and **14** were produced so readily compared with more complicated Koenigs-Knorr type conditions.[9] When the glucopyranosyl bromide **15** [10] was treated under similar conditions it was found (TLC) that little or no glycosidation occurred during a period of 15 hours and that a complex mixture of products were produced gradually over the following 72 hours. Many of these probably resulted from the gradual de-acetylation of the starting material.



1 R_1 = $CH_2CH(OH)CH_2OH$, R_2 = Ac
2 R_1 = $CH_2CH(OH)CH_2OH$, R_2 = Bn
3 R_1 = CH_2CHO, R_2 = H
7 R_1 = $OCH_2CH{=}CH_2$, R_2 = H



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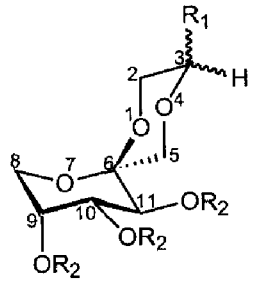
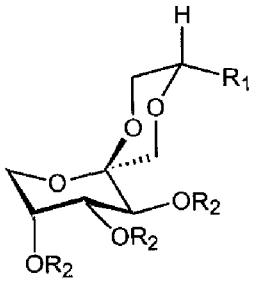
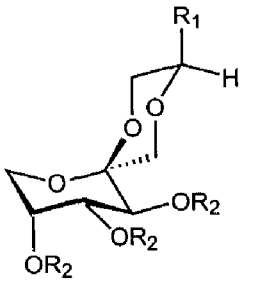


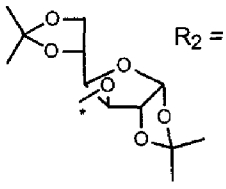
4 R_1 = OH, R_2 = H
6 R_1 = R_2 = H
17 R_1 = OH, R_2 = Ac

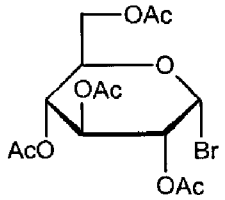


8 R_1 = OAc, R_2 = Ac
10 R_1 = $NHPhNO_2$, R_2 = H
11 R_1 = $NHPhNO_2$, R_2 = Ac
12 R_1 = Br, R_2 = Ac
14 R_1 = OCH_3, R_2 = Ac
16 R_1 = OBzl, R_2 = H
18 R_1 = $NHC(O)CCl_3$, R_2 = Ac



9 R_1 = OAc, R_2 = Ac
13 R_1 = OCH_3, R_2 = Ac
21 R_1 = $NHC(O)CCl_3$, R_2 = Ac

20 R_1 =  R_2 = Ac



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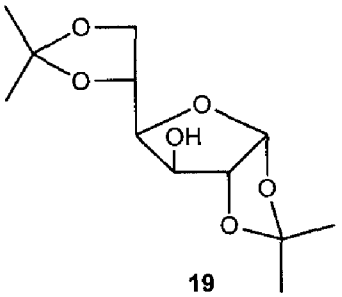

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An alternative procedure for obtaining "quasi" glycosides by alkylation of the C-3 OH group was then investigated. Treatment of compound **4** in aqueous 1,2-dimethoxyethane with

benzyl chloride and potassium hydroxide in the presence of a catalytic quantity of 18-crown-6 at 70°C for 7 hours gave, after column chromatography, the benzyl derivative **16** (71%). The assigned configuration at C-3 was again based on specific rotational and spectral characteristics. It seemed unusual that little alkylation of the fructosyl ring hydroxyl groups had occurred under these conditions. Treatment of **4** with methyl iodide in a similar manner gave, after acetylation of the crude product in the usual manner (acetic anhydride-pyridine), a mixture (GLC) of compounds **13** and **14** in a ratio of 8:1. The mixture was not separated. Acetal syntheses are known [11,12] in which the anion of the hemiacetal is alkylated under basic conditions. Although this approach is not generally used for the synthesis of simple glycosides, a recent study [13] demonstrated that effective glycosidation of several monosaccharides could be achieved under basic conditions using a variety of benzyl bromides. A method of base promoted anomeric *O*-alkylation of protected sugars with alkyl triflates has also been described.[14] A triflate is not always a convenient reagent and the necessity of a suitably blocked substrate also makes this procedure less attractive.

An alternative popular method of glycoside synthesis is the trichloroacetamidate procedure.[15] The stereoselective *O*-activation of the anomeric centre of carbohydrate derivatives as trichloroacetamido compounds normally proceeds easily. Their subsequent reaction with alcohols, including other carbohydrate derivatives under mildly acidic conditions, provides an efficient route to many types of glycosides. It was decided to investigate this approach with derivatives of **3** for obtaining a trisaccharide analogue.

Brief treatment (10 mins) of the bromide **12** with aqueous sodium hydrogen carbonate gave the free hemiacetal **17** in 89% yield as a non-crystalline foam. Treatment of **17** with trichloroacetonitrile in the presence of sodium hydride gave the 3(*R*)-trichloroacetamidate (**18**, 72%) as a syrup. This material was treated with 1,2;5,6-di-*O*-isopropylidene-α-**D**-glucofuranose **19** [16] in the presence of boron trifluoride etherate at -72 C to give crystalline **20** in 32% yield, after column chromatography. When compound **17** was treated with trichloroacetonitrile in the presence of anhydrous potassium carbonate, the alternative (3*S*)-trichloroacetamidate **21** was obtained in 65.5% yield. Reaction of **21** with the diacetal **19** in the above manner also yielded compound **20** (21%) which was identical with the material obtained from the isomeric **18**. The formation of the"α"-linked compound **20** from the two trichloroacetamidates **18** and **21** is not fully understood. Its production from the "β"-linked compound **18** would have been expected,[15] assuming the usual S_N2-type reaction course, whereas from **21** it would require an S_N1-type mechanism. These usually only occur in the presence of polar (donor) solvents and when stronger catalysts are employed. Further studies would be required to clarify these points.

The results obtained during this preliminary study show that the C-3 hemiacetal group of compound **4** behaves in much the same fashion as a normal carbohydrate anomeric group. Further investigations of some of these reactions and the biological evaluation of the products as carbohydrate mimics are in progress.

4.3 Experimental section

For General experimental procedures see Chapter 3.

3,6(S),9(R),10(R),11(S)-1,4,7-trioxaspiro[5,5]undecane-3,9,10,11-tetrol (4)

A stirred, cooled (-78°C) solution of allyl β-D-fructopyranoside (**7**, 18.0 g, 82 mmol) in water (45 mL) and methanol (450 mL) was subjected to ozonolysis until analysis (TLC, dichloromethane-methanol, 4:1) indicated the absence of compound **7** and a permanent blue colouration had developed. Nitrogen gas was then bubbled through the mixture for *ca* 10 mins, whereon it was treated with triphenylphosphine (21.48 g, 82 mmol), set aside at -78°C for 30 mins, and then allowed to attain room temperature gradually. The mixture was concentrated *in vacuo*, treated with water (100 mL), set aside at 5°C for 18 hr, during which time triphenylphosphine oxide (23.0 g) crystallized out and which was collected by filtration and washed with water (100 mL). The combined filtrate and washings were concentrated *in vacuo* and the resultant crystalline material was recrystallized from ethanol to yield pure **4** (15.9 g, 87.5%), m.p. 172.5-174.5°C, $[\alpha]_D$ –125° (H_2O, constant after 24 hr). ^{13}C-NMR (D_2O, 75 MHz) δ 97.20, 96.29, 92.07, 88.71, 70.41, 70.19, 70.12, 69.40, 68.18, 64.64, 64.57, 63.61, 63.13, 60.99 ppm. ^{1}H-NMR (D_2O, 300 MHz) δ: 4.96 (d, 0.42H, J = 1.9 Hz, H-3_{ax}), 4.89 (dd, 0.58H, J = 2.9 and J = 9.2 Hz, H-3_{eq}), 4.29 (d, 0.42H, J = 12.1 Hz, H-11_{ax}), 3.99 (d, 0.58H, J = 12.3 Hz, H-11_{eq}), 3.94 - 3.32 (m, 8H, remaining H) . *Anal.* calc. for $C_8H_{14}O_7$: C, 43.25; H, 6,35. Found: C. 42.77; H, 6.28%.

[#] The equatorial/axial proton ratios varied with time.

3(R),6(S),9(R),10(R),11(S)-3,9,10,11-tetra-acetoxy- and 3(S),6(S),9(R),10(R),11(S)-3,9,10,11-tetra-acetoxy-1,4,7-trioxaspiro[5,5]undecanes (8) and (9)

A cooled (0°C), stirred solution of compound **4** (9.30 g, 42 mmol) in dry pyridine (100 mL) was treated with acetic anhydride (80 mL), set aside at room temperature for 20 hr and processed in the usual manner. A solution of the resultant material in ether (100 mL) was set aside (2 hr), and the resultant material collected by filtration. Analysis (GLC) of the material indicated a mixture of compounds **8** and **9** (1:2). Column chromatography (hexane-ethyl acetate, 3:2) of a portion (1.06 g) of the foregoing product gave compound **9** (0.695 g, 52%), m.p. 160.5-162°C (aqueous MeOH), $[\alpha]_D$ –177° ($CHCl_3$). ^{13}C-NMR ($CDCl_3$, 75 MHz,): δ 170.33 (2x), 169.95, 164.41, 95.55, 88.81, 68.88, 68.54, 67.63, 65.76, 61.82, 59.66, 20.94 (2x), 20.70, 20.61 ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 5.93 (dd, 1H, $J_{3,2a}$ = 8.7 Hz, $J_{3,2b}$ = 4.7 Hz, H-3), 5.39-5.27 (m, 3H, H-9, H-10, H-11), 4.02-3.66 (m, 6H), 2.15-1.99 (4s, each 3H, acetyl H). *Anal.* calc. for $C_{16}H_{22}O_{11}$: C, 49.23; H, 5.68. Found: C, 49.34; H, 5.65%.

Continued elution then gave material that was a mixture (GLC), followed by compound **8** (144 mg, 11%), m.p. 171-172.5°C (aqueous ethanol), $[\alpha]_D$ –79° ($CHCl_3$). ^{13}C-NMR (75 MHz, $CDCl_3$):δ 170.24, 170.08, 169.78, 169.35, 95.16, 87.62, 68.86, 67.43, 67.36, 61.56, 61.49, 60.91, 20.86 (2x), 20.60 and 20.52 ppm. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 5.92 (d, 1H, J = 1.8 Hz, H-3), 5.41 (dd, 1H, $J_{10,11}$ = 10.3 Hz and $J_{10,9}$ = 3.5 Hz), 5.37 (m, 1H, H-9), 5.19 (d, 1H, $J_{11,10}$ = 10.3 Hz, H-11), 4.06 (dd, 1H, $J_{2a,2b}$ = 12.3 Hz and $J_{2a,3}$ = 2.1 Hz, H-2a), 3.92 (dd, 1H, $J_{8a,8b}$ = 13.1 Hz and $J_{8a,9}$ = 1.3 Hz, H-8a), 3.87 (d, 1H, J = 12 Hz, H-5a), 3.85 (dd, 1H, $J_{8b,8a}$ = 13.1 Hz and

$J_{8b,9}$ = 1.7 Hz, H-8b), 3.76 (d, 1H, J = 12.3 Hz, H-2b), 3.57 (d, 1H, J = 12.0 Hz, H-5b), 2 (4s, each 3H, acetyl H). Anal. calc. for $C_{16}H_{22}O_{11}$: C, 49.23; H, 5.68. Found: C, 48.99; H, 5.64%.

Colourless transparent crystals of **8** suitable for X-ray diffraction studies were obtained from ethyl acetate solution by slow evaporation of the solvent. Colourless transparent crystals of **9** suitable for X-ray diffraction studies were obtained from a methanol / water solution by slow cooling of the solvent. A single crystal was mounted in air on a glass fibre. Intensity data were collected at room temperature. An Enraf-Nonius CAD4 single-crystal diffractometer was used, Cu-Kα radiation (λ=1.54184 Å), θ-2θ scan mode. Unit cell dimensions were determined from the angular setting of 25 reflections. Intensity data were corrected for Lorentz and polarization effects. Semi-empirical absorption correction (psi-scans) [18] was applied.

Crystal data for compound **9**: (see Table 2) $C_{16}H_{22}O_{11}$, Mr = 390.34, orthorhombic, spacegroup $p^2_1^2_1^2_1$, a=8.0281(2), b=9.2525(2), c=25.4333(5), V=1889.19(8)Å^3, Z=4, ρ(calcd) =1.372g/cm^3.

Crystal data for compound **8**: (see Table 1) $C_{16}H_{24}O_{12}$, Mr = 408.35, monoclinic, spacegroup p^2_1, a=8.7436(3), b=7.89530(18), c=14.6467(4), V=986.67(5)Å^3, Z=2, ρ(calcd) =1.374g/cm^3.

The structures were solved by the program CRUNCH [19] and was refined with standard methods (refinement against F^2 of all reflections with SHELXL97 [17] with anisotropic parameters for the nonhydrogen atoms. The hydrogen atoms of the methyl groups were refined as rigid rotors with idealized sp^3 hybridization and a C-H bond length of 0.97 Å to match maximum electron density in a difference Fourier map. All other hydrogens were initially placed at calculated positions and were freely refined subsequently.

Final *R*-indices for **9**: R_1=0.0322 (for 1905 reflections considered observed [I>2σ(I)]), wR_2=0.0914 (all data) for all 289 parameters.

Final *R*-indices for **8**: R_1=0.0492 (for 1995 reflections considered observed [I>2σ(I)]), wR_2=0.1499 (all data) for all 298 parameters.

PLUTON drawings [20] of the X-ray structures are shown in Figs. 1 and 2.

*3(**R**),6(**S**),9(**R**),10(**R**),11(**S**)-3-p-Nitrophenylamino-1,4,7-trioxaspiro[5,5]undecane-9,10,11-triol (**10**)*

A stirred solution of compound **4** (0.9 g, 4.05 mmol) in ethanol (10 mL) was treated with *p*-nitroaniline (0.55 g, 4.05 mmol) and glacial acetic acid (0.5 mL) and heated at 70°C for 30 min, The mixture was concentrated *in vacuo* to *ca* half volume, set aside at room temperature for 1 week, and the crystalline material collected by filtration, washed with a small volume (*ca* 4 mL) of ethanol to give compound **10** (1.124 g, 81%), m.p. 223°C, $[\alpha]_D$ +281° (CH_2Cl_2 - MeOH, 1:1). ^{1}H-NMR (DMSO-D_6, 300 MHz,): δ 8.05 (d, 2H, J = 9.2 Hz, aromatic H), 7.96 (d, 1H, J = 6.6 Hz, N*H*), 6.88 (d, 2H, J = 9.2 Hz, aromatic H), 5.03 (dd, 1H, J = 6.3 Hz and J = 2.5 Hz, H-3), 4.64 (d, 1H, J = 5.9 Hz, O*H*), 4.58(d, 1H, J = 3.7 Hz, O*H*), 4.45 (d, 1H, J = 8.2 Hz, O*H*), 4.02 (m, 2H), 3.71 (m, 1H), 3.64-3.51 (m, 4H), 3.30-3.15 (m, 2H). *Anal.* calc. for $C_{14}H_{18}N_2O_8$: C, 49.12; H, 5.30; N 8.18. Found: C, 49.12; H 5.36; N, 8.01%.

*3(**R**),6(**S**),9(**R**),10(**R**),11(**S**)-3-p-Nitrophenylamino-9,10,11-triacetoxy-1,4,7-trioxaspiro[5,5] undecane (**11**)*

A sample (165 mg) of the foregoing material in anhydrous pyridine (1.5 mL) was treated with acetic anhydride (1 mL), stored overnight at room temperature, and processed in the usual manner to give **11** (148 mg, 65.5%), m.p. 188-197°C (ethanol), $[\alpha]_D$ = -151° ($CHCl_3$). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 170.27, 169.95, 169.67, 150.45, 139.82, 126.12 (2x), 112.61 (2x), 95.54, 75.23, 68.85, 67.55, 67.39, 62.24, 61.57, 59.90, 20.89, 20.60, 20.56 ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.13 (m, 2H, aromatic H), 6.78 (m, 2H, aromatic H), 5.62 (d, 1H, J = 7.2 Hz, N-*H*), 5.41 (dd, 1H, J = 3.5 Hz and J = 10.3 Hz, H-10), 5.30 (m, 1H, H-9), 5.18 (d, J = 10.3 Hz, H-11), 5.07 (dd, 1H, J = 2.4 Hz and J = 11.7 Hz, H-3), 4.29 (dd, 1H, J = 2.7 Hz and J = 11.7 Hz, H-2a), 3.95 (dd, 1H, J = 1.3 Hz and J = 13.1 Hz, H-8a), 3.87 (dd, 1H, J = 13.1 Hz, J = 1.3 Hz, H-8b), 3.74 (d, 1H, J = 11.6 Hz, H-2b), 3.72 (d, 1H, J = 12.4 Hz, H-5a), 3.47 (d, 1H, J = 12.4 Hz, H-5b), 2.17-2.00 (3s, each 3H, acetyl H). *Anal.* calc. for $C_{20}H_{22}N_2O_{11}$: C, 51.28; H, 5.10; N, 5.98. Found: C, 51.44; H, 5.13; N, 5.96%.

*3(**R**),6(**S**),9(**R**),10(**R**),11(**S**)-3-Bromo-9,10,11-triacetoxy-1,4,7-trioxospiro[5,5]undecane (**12**)*

A stirred solution of a mixture of compounds **8** and **9**, *vide supra*, (0.5 g) in 33% hydrogen bromide solution in glacial acetic acid (0.5 mL) was maintained at room temperature for 10-15 mins. The mixture was treated with dichloromethane (30 mL) and ice-water (20 mL). The separated organic layer was washed sequentially with ice cold saturated aqueous sodium hydrogen carbonate solution and ice-water, dried (Na_2SO_4) and concentrated *in vacuo* to give **12** (0.49 g, 94%) as a syrup, $[\alpha]_D$ –39° ($CHCl_3$). ^{1}H-NMR ($CDCl_3$, 100 MHz): δ 6.37 (d, 1H, J = 17 Hz, H-3), 5.40-5.10 (m, 3H, H-9, 10, 11), 4.27 (dd, 1H, J = 2 Hz and J = 12 Hz, H-2), 4.13-3.53 (m, 5H), 2.20-2.00 (3s, each 3H, acetyl H).

*3(**S**),6(**S**),9(**R**),10(**R**),11(**S**)-3-Methoxy-9,10,11-triacetoxy-1,4,7-trioxaspiro[5,5]undecane (**13**) and 3(**R**),6(**S**),9(**R**),10(**R**),11(**S**)-3-methoxy-9,10,11-triacetoxy-1,4,7-trioxaspiro[5,5]undecane (**14**)*

A mixture of compounds **8** and **9** (1.0g, 2.56 mmol) was treated and processed as described above and the resulting compound **12** (1.05g, 100%), treated with methanol (20 mL) followed by anhydrous sodium carbonate (1.03 g) and then allowed to stir at room temperature for 30 mins. The mixture was diluted with dichloromethane (20 mL), filtered, the organic layer washed with dichloromethane (10 mL) and the combined filtrate and washings concentrated *in vacuo*. Column chromatography (hexane - ethyl acetate, 2:1) gave compound **13** (448 mg, 48%), m.p. 133.5-135°C (di-isopropylether) $[\alpha]_D$ –199° ($CHCl_3$). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 170.31 (2x), 169.89, 97.18, 95.46, 68.98, 68.62, 67.74, 64.96, 61.59, 61.13, 55.84, 20.92, 20.72 and 20.59 ppm.^{1}H-NMR ($CDCl_3$, 300 MHz): δ 5.35 (m, 2H, H-9, 10), 5.27 (d, 1H, J = 10,1 Hz, H-11), 4.61 (dd, 1H, $J_{3,4a}$ = 13.2 Hz and $J_{3,4b}$ = 8.4 Hz, H-3), 3.96 (dd, 1H, $J_{8a,8b}$ = 13.2 Hz and $J_{8a,9}$ = 1.2 Hz, H-8a), 3.77 (m, 3H, H-8b, 2a, 5), 3.68 (d, 1H, J = 12.4 Hz, H-5b), 3.53 (dd, 1H, $J_{2b,3}$ = 8.4 Hz and $J_{2b,2a}$ = 11.6 Hz, H-2b), 3.45 (s, 3H, O*CH*$_3$), 2.15-1.99 (3s, each 3H, acetyl H). *Anal.* calc. for $C_{15}H_{22}O_{10}$: C, 49.72; H, 6.12. Found: C, 49.91; H, 6.06%.

Continued elution then gave **14** (192 mg, 21%) which was recrystallized from aqueous propan-2-ol, m.p. 174.5-175°C, $[\alpha]_D$ -56.8° ($CHCl_3$). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 170.45, 170.29, 169.77, 95.24, 94.34, 69.04, 67.62, 67.52, 61.93, 61.38, 59.91, 55.12, 20.90, 20.73, 20.54 ppm. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 5.39 (m, 2H, H-9, 10), 5.19 (d, 1H, $J_{11,10}$ = 10.2 Hz, H-11), 4.53 (d, 1H, J = 2.0 Hz, H-3), 3.96 (dd, 1H, $J_{2a,3}$ = 2.2 Hz and $J_{2a,2b}$ = 11.8 Hz, H-2a), 3.93 (dd, 1H, $J_{8a,9}$ = 1.4 Hz and $J_{8a,8b}$ = 13.1 Hz, H-8a), 3.85 (dd, 1H, $J_{8b,9}$ = 1.7 Hz and $J_{8b,8a}$ = 13.1 Hz, H-8b), 3.81 (d, 1H, J = 11.8 Hz, H-5a), 3.71 (d, 1H, J = 11.8 Hz, H-2b), 3.46 (d, 1H, J = 11.8 Hz, H-5b), 3.43 (s, 3H, OC*H*$_3$), 2.16-1.98 (3s, each 3H, acetyl H). *Anal.* calc. for $C_{15}H_{22}O_{10}$: C, 49.72; H, 6.12. Found: C, 49.89; H, 6.05%.

*3(**S**),6(**S**),9(**R**),10(**R**),11(**S**)-3-Benzyloxy-1,4,7-trioxaspiro[5,5]undecane -9,10,11-triol (**16**)*

A stirred solution of compound **4** (223 mg, 1 mmol) in 1,2-dimethoxyethane (5 mL) and water (5 mL) was treated sequentially with potassium hydroxide (156 mg, 2.78 mmol), benzyl chloride (0.25g, 1.97 mmol) and 18-crown-6 (5 mg). The mixture was maintained at 70°C for 7 hr, set aside at room temperature for 50 hr, diluted with water (40 mL), extracted with ether (2x 20 mL), and the aqueous layer concentrated *in vacuo*. Column chromatography (dichloromethane - methanol, 6:1) gave compound **16** (222 mg, 71%), m.p. 147.5-151.5°C (ethyl acetate), $[\alpha]_D$ –201° ($CHCl_3$). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 137.08 (1x), 128.38 (2x), 127.82 (3x), 95.86, 95.69, 70.05 (2x), 69.70, 69.21, 66.17, 63.53 and 61.73 ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.31 (m, 5H, aromatic H), 4.87 (d, 1H, J = 11.8 Hz, benzylic H), 4.79 (dd, 1H, J = 4.5 Hz and J = 8 Hz, H-3), 4.58 (d, 1H, J = 11.8 Hz, benzylic H), 3.98 (m, 2H), 3.87-3.77 (m, 4H), 3.73-3.58 (m, 3H) ppm. *Anal.* calc. for $C_{15}H_{20}O_7$: C, 57.69; H, 6.45. Found: C, 57.56; H, 6.46%.

*3(**R**),6(**S**),9(**R**),10(**R**),11(**S**)-3-Hydroxy-9,10,11-triacetoxy-1,4,7-trioxaspiro[5,5]undecane (**17**)*

A stirred solution of the bromide **12** (493 mg, 12 mmol) in 1,2-dimethoxyethane (10 mL) was treated with sodium hydrogen carbonate (120 mg) followed by water (1 mL) and then set aside at room temperature for 10 mins when analysis (TLC, hexane-ethyl acetate, 1:1) indicated the absence of **17**. The mixture was treated with dichloromethane (20 ml), dried (Na_2SO_4) and concentrated *in vacuo* to give **17** (372 mg, 89%) as a foam, $[\alpha]_D$ -117° (ethanol, 1 min). ^{13}C-NMR ($CDCl_3$, 25 MHz): δ 170.38, 170.28, 169.25, 95.27, 94.53, 90.64, 78.35, 77.08, 75.81, 68.93, 67.76, 67.67, 67.51, 65.90, 62.69, 62.35, 61.29, 59.81, 20.57, 20.54 and 20.44 ppm. ^{1}H-NMR ($CDCl_3$, 100 MHz): δ 5.45-5.15 (m, 3H, H-9, 10, 11), 5.13-4.85 (m, 1H, H-3), 4.09-3.39 (m, 6H, H-2a, 2b, 5a, 5b, 8a, 8b), 2.16-1.99 (3s, each 3H, acetyl H) ppm.

*3(**R**),6(**S**),9(**R**),10(**R**),11(**S**)-9,10,11-triacetoxy-3-Trichloroacetamido-1,4,7-trioxaspiro[5,5] undecane (**18**)*

A stirred solution of compound **17** (650 mg, 1.87 mmol) in dry acetonitrile (10 mL) was treated sequentially with trichloroacetonitrile (0.65 mL) and sodium hydride (63 mg, 2.63 mmol) and set aside at room temperature for 20 mins. The mixture was filtered through a layer (*ca* 1 cm) of silica gel, the inorganic material washed with acetonitrile (2x 5 mL) and the combined filtrate and washings concentrated *in vacuo*. Column chromatography (hexane-ethylacetate, 1:1)

of the resultant material yielded compound **18** (665 mg, 72%) as a foam, $[\alpha]_D$ –55° ($CHCl_3$). ^{1}H-NMR ($CDCl_3$, 100 MHz): δ 8.64 (bs, 1H, NH), 6.08 (bs, 1H, H-3), 5.50-5.07 (m, 3H, H-9, 10, 11), 4.23-3.55 (m, 6H, residual H), 2.17-1.99 (3s, each 3H, acetyl H) ppm.

*3(**S**),6(**S**),9(**R**),10(**R**),11(**S**)-9,10,11-Triacetoxy-3-trichloroacetamido-1,4,7-trioxaspiro-[5,5]undecane (21)*

A stirred mixture of compound **17** (530 mg, 1.52 mmol) and anhydrous potassium carbonate (536 mg) in dichloromethane (10 mL) was treated with trichloroacetonitrile (770 mg, 5.33 mmol). The mixture was set aside at room temperature for 6 hr, filtered, the inorganic material washed with dichloromethane (2x 5 mL), and the combined filtrate and washings concentrated *in vacuo*. Column chromatography (hexane-ethyl acetate-triethylamine, 50:50:1) of the crude product gave **21** (492 mg, 65.5%), $[\alpha]_D$ -154.5° ($CHCl_3$). ^{1}H-NMR ($CDCl_3$, 100 MHz): δ 8.64 (s, 1H, NH), 6.20 (dd, 1H, J = 5.6 Hz and J = 8.1 Hz, H-3), 5.37 (bs, 3H, H-9, 10, 11), 4.23-3.71 (m, 6H, residual H), 2.16-2.00 (3s, each 3H, acetyl H) ppm.

*3(**R**),6(**S**),9(**R**),10(**R**),11(**S**)-3-O-(1',2',5',6'-Di-O-isopropylidene-α-**D**-glucofurano-3'-yl)-9,10,11-triacetoxy-1,4,7-trioxaspiro[5,5]undecane (20)*

A stirred, cooled (-78 C) mixture of compound **18** (665 mg, 1.35 mmol), 1,2;5,6-di-O-isopropylidene α-**D**-glucofuranose (**19**, 351 mg, 1.35 mmol) [16] and molecular sieves 3Å (1.0 g), maintained under N_2, was treated with 0.1**M** boron trifluoride in dichoromethane (3.37 ml, 0.25 eq). The mixture was allowed to stir at the same temperature for 3 hr when potassium carbonate (400 mg), followed by dichloromethane (20 mL) and saturated sodium hydrogen carbonate solution (10 mL) were added and the mixture allowed to attain room temperature. The mixture was then filtered, the inorganic material washed with dichloromethane (2x 5 mL), the combined filtrate and washings were separated and the aqueous layer extracted with dichloromethane (10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to give an oil (980 mg). Column chromatography (hexane-ethyl acetate, 2:1) of this material gave compound **19** (195 mg), m.p. 109-111°C, $[\alpha]_D$ -18° ($CHCl_3$), lit [16]. m.p. 110°C, $[\alpha]_D$ -18.8° ($CHCl_3$) followed by compound **20** (255 mg, 32%) obtained as an oil which was crystallized from di-isopropyl ether (196 mg, 25%), m.p. 151-153.5°C, $[\alpha]_D$ –41° ($CHCl_3$). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 170.33, 170.27, 169.82, 112.14, 109.20, 105.24, 95.19, 94.16, 84.05, 81.34, 80.34, 72.46, 68.99, 67.73, 67.72, 67.53, 61.77, 61.44, 60.52, 26.90, 26.81, 26.27, 25.34, 20.95, 20.63 and 20.58 ppm. ^{1}H-NMR (400 MHz, $CDCl_3$, 25 C): δ 5.85 (d, 1H, J = 3.6 Hz, H-1'), 5.39 (dd, 1H, $J_{10,9}$ = 3.5 Hz and $J_{10,11}$ = 10.4 Hz, H-10), 5.36 (m, 1H, H-9), 5.17 (d, 1H, $J_{11,10}$ = 10.4 Hz, H-11), 4.91 (d, 1H, $J_{3,2a}$ = 2.1Hz, H-3), 4.51 (d, 1H, $J_{2',1'}$ = 3.6 Hz, H-2'), 4.27 (d, 1H, $J_{3',4'}$ = 2.9 Hz, H-3'), 4.20 (m, 1H, H-5'), 4.12 (dd, 1H, $J_{6'a,6'b}$ = 8.6 Hz and $J_{6'a,5'}$ = 6.0 Hz, H-6'a), 4.08 (dd, 1H, $J_{4',3'}$ = 2.9 Hz and $J_{4',5'}$ = 8.6 Hz, H-4'), 3.98 (dd, 1H, $J_{6'b,5'}$ = 5.2 Hz and $J_{6'b,6'a}$ = 8.6 Hz, H-6b), 3.93 (dd, 1H,$J_{2a,3}$ = 2.3 Hz and $J_{2a,\ 2b}$ = 11.7 Hz, H-2a), (at 40 C), 3.90 (dd, 1H, $J_{8a,9}$ = 1.1 Hz, H-8a), 3.83 (d, 1H, $J_{5a,5b}$ = 11.8 Hz, H-5a), 3.82 (dd, 1H, $J_{8a,8b}$ = 13.1 Hz and $J_{8b,9}$ = 1.8 Hz, H-8b), (at 25 C), 3.70 (d, 1H, $J_{2b,2a}$ = 1.7 Hz, H-2b), 3.51 (d, 1H, J = 11.8 Hz, H-5b), 2.17-1.98 (3s, each 3H, acetyl H), 1.50-1.31 (4s, each 3H, CMe_2) ppm. Anal calcd. for $C_{26}H_{38}O_{15}$: C, 52.88, H, 6.49. Found: C, 52.62; H, 6.55%.

In another experiment the trichloroacetamidate **21**, *vide supra*, (232 mg, 0.471 mmol) was reacted with compound **19** (122 mg, 0.471 mmol) in the presence of boron trifluoride etherate and processed in the manner described above to give compound **20** (118 mg, 42%). The physical and spectral data were identical to that for compound **20** described above.

Crystallographic data (excluding structure factors) for the structures reported in this chapter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no CCDC-101081.

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4.5 Appendix

Table 1: Crystal data and structure refinement for **8**.

Identification code	Compound **8**
Empirical formula	$C_{16}H_{24}O_{12}$
Formula weight	408.35
Temperature	293(2) K
Crystal system, space group	Monoclinic, P 2_1
Unit cell dimensions (25 reflections)	$36.525 < \theta < 45.359$)
	a = 8.7436(3) Å $\alpha = 90°$
	b = 7.89530(18) Å $\beta = 102.623(9)°$
	c = 14.6467(4) Å $\gamma = 90°$
Volume	986.67(5) $Å^3$
Z, Calculated density	2, 1.374 Mg/m^3
Absorption coefficient	1.034 mm^{-1}
Diffractometer/scan	Enraf-Nonius CAD4/θ-2θ
Radiation/wavelength	Cu-Kα (graphite monochr.)/1.54184 Å
F(000)	432
Crystal size	0.54 x 0.21 x 0.08 mm
θ range for data collection	3.09 - 69.88°
Index ranges	0<=h<=10, 0<=k<=9, -17<=l<=17
Reflections collected	2117
Independent/observed reflections	1995 (R_{int} =0.0140)/1884([Io>2σ(Io)])
Absorption correction	Semi-emperical from psi-scans [18]
Range of relat. transm. Factors	0.973 and 1.053
Refinement method	Full-matrix least-squares on F^2
Computing	SHELXL-97 [17]
Data / restraints / parameters	1995 / 1 / 298
Goodness-of-fit on F^2	1.057
SHELXL-97 weight parameters	0.1155 0.1449
Final R indices [I>2σ(I)]	$R_1 = 0.0492$, $wR_2 = 0.1468$
R indices (all data)	$R_1 = 0.0513$, $wR_2 = 0.1499$
Extinction coefficient	0.010(2)
Largest diff. peak and hole	0.278 and -0.475 e. $Å^{-3}$

Table 2: Crystal data and structure refinement for **9**.

Identification code	Compound **9**
Empirical formula	$C_{16}H_{22}O_{11}$
Formula weight	390.34
Temperature	293(2) K
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Unit cell dimensions (25 reflections)	$40.242 < \theta < 46.196$)
	a = 8.0281(2) Å $\alpha = 90°$
	b = 9.2525(2) Å $\beta = 90°$
	c = 25.4333(5) Å $\gamma = 90°$
Volume	1889.19(8) $Å^3$
Z, Calculated density	4, 1.372 Mg/m^3
Absorption coefficient	1.016 mm^{-1}
Diffractometer/scan	Enraf-Nonius CAD4/θ-2θ
Radiation/wavelength	Cu-Kα (graphite monochr.)/1.54184 Å
F(000)	824
Crystal size	0.59 x 0.21 x 0.08 mm
θ range for data collection	3.48 - 69.87°
Index ranges	0<=h<=9, -11<=k<=0, 0<=l<=30
Reflections collected	2069
Independent/observed reflections	2069/1905([Io>2σ(Io)])
Absorption correction	Semi-emperical from psi-scans [18]
Range of relat. transm. Factors	0.931 and 1.145
Refinement method	Full-matrix least-squares on F2
Computing	SHELXL-97 [17]
Data / restraints / parameters	2069 / 0 / 289
Goodness-of-fit on F^2	1.049
SHELXL-97 weight parameters	0.0526 0.3441
Final R indices [I>2σ(I)]	$R_1 = 0.0322$, wR_2 0.0884
R indices (all data)	$R_1 = 0.0355$, $wR_2 = 0.0914$
Extinction coefficient	0.0068(5)
Largest diff. peak and hole	0.169 and -0.159 e. $Å^{-3}$

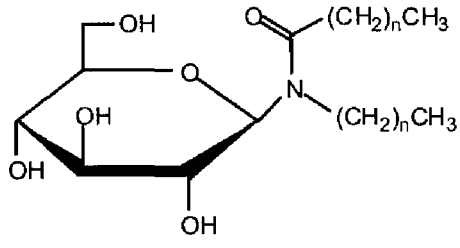
CHAPTER 5

SYNTHESIS OF SOME ACYLAMINO DERIVATIVES FROM 2(*R*),3-DIHYDROXYPROPYL β-D-FRUCTOPYRANOSIDE [1-*O*-β-D-FRUCTOPYRANOSYL-*sn*-GLYCEROL]

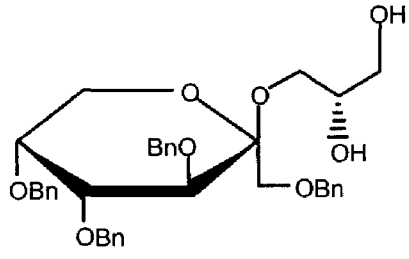
5.1 Introduction

There is considerable current interest in the development of amphiphilic molecules based on natural products, e.g. carbohydrates and amino acids, for use in various areas of medicine. [1,2] The object of these studies is to develop liposome-like materials that can stimulate or penetrate natural lipid layers in cells as vectors for drug transportation. A key factor in the drug disposition is their "lipophilicity", i.e. the ability to diffuse passively through biological membranes.[3] The coupling or encapsulation of drugs to lipophiles would be a useful application of these materials. These include ordinary pharmaceuticals but more importantly genetic material and other nucleic acid based derivatives such as anti-sense oligonucleotides for gene therapy. Gene therapy presents a real opportunity of curing disease, rather than merely treating the symptoms.

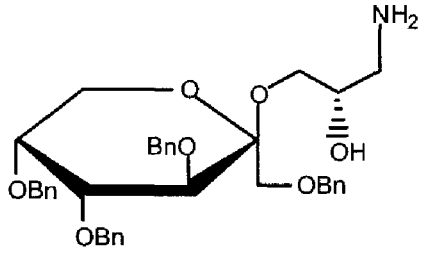
Some of the newly developed [4] molecules, e.g. **1**, have long-chain *N*-acyl amino groups as part of their structures and show a formal resemblance to sphingolipid-type structures. These derivatives may have application in the specific immunisation of selected carbohydrate antigens. [4]



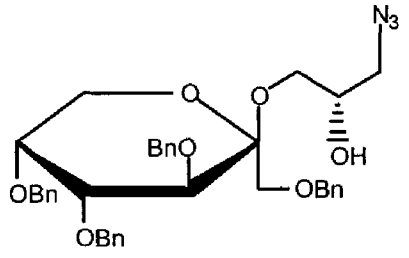
1



2



3



4

The importance of some glycolipids in the mechanism of cell-cell recognition and the role played in the growth and differentiation of tissue is well known.[5] The free diol group of compound **2** (Chapter 3) would permit the ready introduction of an amino substituent under

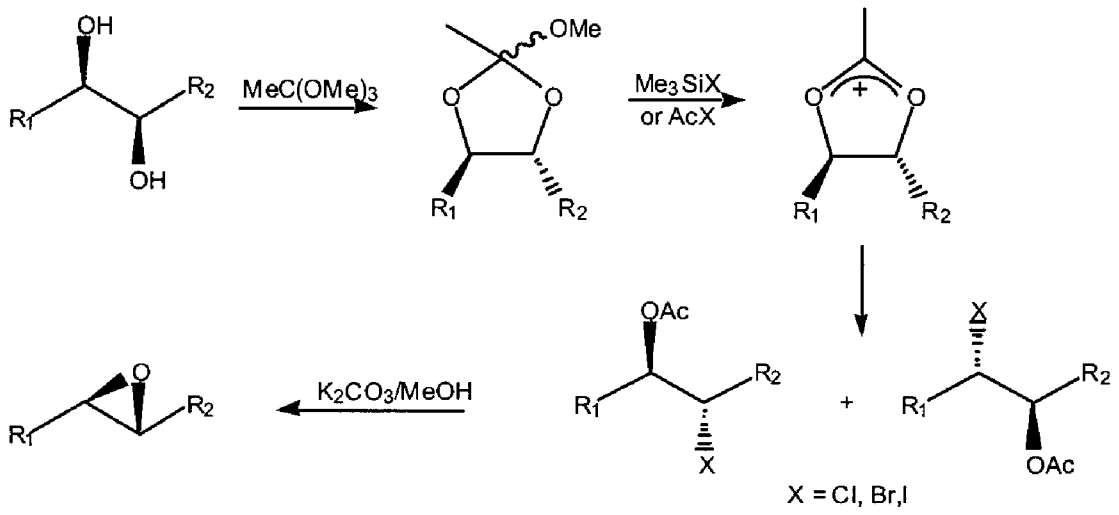
simple conditions. This could lead to the formation of a variety of interesting "lipid" type structures bearing long-chain *N*-acyl / and *O*-acyl functions. The synthesis of some of these derivatives based on the amino alcohol **3** forms the basis of this chapter.

Compound **3** was obtained by two main synthetic routes based on the utilization of a cyclic sulfate or an oxirane intermediate to yield the azido alcohol **4** which gave the amino alcohol **3** on reduction.

Oxiranes are important, versatile intermediates which easily undergo stereospecific ring-opening reactions to give bi-functional products.[6] There are several known procedures for obtaining these epoxides, most of which show poor enantioselectivity. These include [6] the oxidation of alkenes by organic peracids and reactions [7] of alkenes with hydrogen peroxide in the presence of transition metal catalysts. Some of these reactions are used industrially.[8]

One of the most useful developments in the field of organic asymmetric synthesis was the introduction of enantioselective epoxidation of allylic alcohols in the presence of optically active tartrate esters (Sharpless epoxidation).[9,10] The substrate requirement for these reactions is fairly rigid. Optically active oxiranes play a very important role in modern synthetic organic chemistry. They represent electrophilic chiral building blocks with unnatural 1, 2 group functionality. The stereospecific conversion of enantiomerically defined vicinal diols into the corresponding oxiranes has much wider appeal.[11,12] Some of these transformations result in overall retention of configuration of the starting material, others with net inversion, depending on the reaction conditions and reagents employed.

A traditional route to oxiranes is *via* sulfonate ester intermediates. These reactions have been of particular importance in carbohydrate chemistry for the synthesis of oxirane derivatives of aldoses and aldosides.[13] The standard procedure is based on the treatment of sulfonate esters having vicinal hydroxyl groups, which are free or esterified, with a strong base. Methanesulfonic or *p*-toluenesulfonic esters are commonly used. Selective manipulation of a diol group is based [14,15] in most cases on steric or electronic effects, which influence the relative acidities of the groups involved, and hence reactivity.[16-18] A primary hydroxyl group is usually more easily substituted than a secondary one in a diol system comprised of both types.



Scheme 5.1: General synthesis of oxiranes from diols via cyclic orthoacetates.

An alternative synthetic procedure is based on the formation of cyclic orthoester intermediates,[12,19,20] which on treatment with an acyl halide or halosilane results in the formation of an acylated halohydrin derivative, presumably *via* an acetoxonium ion. These two steps are often conducted as a sequential "one pot" process. Treatment of the product with base yields the oxirane (scheme 5.1).

The opening of the intermediate is usually highly regioselective. The nucleophile is introduced mainly at the least hindered carbon atom, or away from an inductively electron-withdrawing function. The transformation of a terminal diol into an oxirane using this approach results in overall retention of configuration of the stereogenic centre.

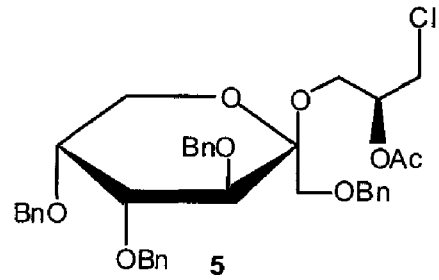
Cyclic sulfites and sulfates share many of the beneficial properties of oxiranes with the added advantage that they are sometimes more reactive to attack by nucleophiles. They can be regarded as synthetic equivalents of oxiranes and many useful applications have been reported over recent years, especially in various areas of carbohydrate chemistry, *inter alia*.[22-27] In most cases cyclic sulfites react similarly to cyclic sulfates. They can be opened at either carbon centre by nucleophiles, but they are usually less reactive. Cyclic sulfites are readily obtained by reaction of a suitable diol with thionyl chloride in the presence of a base at 0°C. The analogous reaction of diol with sulfuryl chloride usually results in low yields of cyclic sulfates.[28-30] These are, however, readily available by oxidation of cyclic sulfites. Stoichiometric quantities of conventional oxidants, e.g. potassium permanganate were used originally for this purpose, but this has now been superseded by a superior "one-pot" process using a catalytic quantity of ruthenium tetroxide in the presence of sodium metaperiodate.[12]

5.2 Synthesis of 2(*R*)-Hydroxy-3-azidopropyl 1',3',4',5'-tetra-*O*-benzyl-β-D-fructopyranoside

5.2.1 ... *via* an oxirane intermediate

Reaction of the protected diol **2** with a mixture of triethyl*ortho*acetate and trimethylchlorosilane in dichloromethane at 0°C gave the 2-*O*-acetyl-3-chloropropyl glycoside **5** in excellent yield (89-94%) after chromatographic purification. Compound **5** was further characterized as the crystalline unprotected compound **6** by catalytic hydrogenolysis (H_2, Pd/C) in the usual manner. Treatment of product **5** with potassium carbonate in methanol gave the oxirane **7** (68%). Similarly, treatment of **5** with a methanolic solution of sodium methoxide gave **7** in 73% yield.

The formation of the oxirane **7** by an alternative route was then investigated. Reaction of the diol with one equivalent of *p*-toluenesulfonyl chloride-pyridine in the usual manner gave the mono-ester **8** in 79% yield. Treatment of the product with methanolic sodium methoxide resulted in the formation of compound **7** in 33% overall yield.



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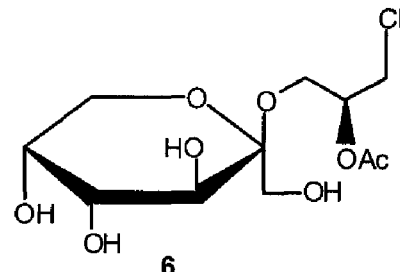

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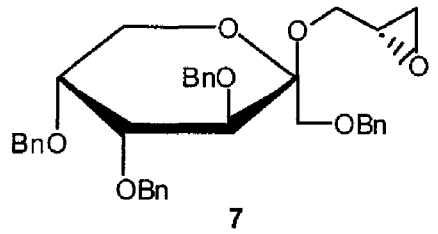

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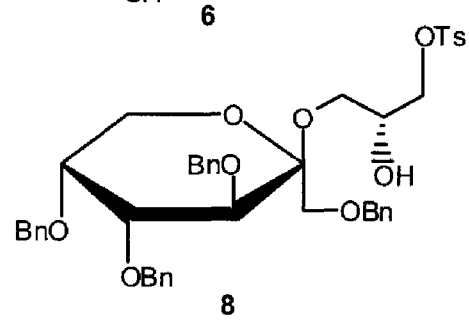

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Nucleophilic ring opening of oxiranes with azide ions is one of the main synthetic routes for the synthesis of amino sugar.[13, 31-34] The use of sodium azide alone is not always satisfactory, due to the slightly alkaline conditions generated during the reaction. Ammonium chloride or sulfate are normally employed to buffer the reaction mixture and to aid in the solubilization of sodium azide.[13]

The formation of the azido alcohol **4** from compound **7** was achieved using a mixture of sodium azide / ammonium sulfate in aqueous 2-methoxyethanol at room temperature for 3-4 days.[35,36] The yield of the pure product (84%) after column chromatography was higher than when the reaction was performed at 50°C for 24 hours (75%). When the reaction was carried out in aqueous 1,4-dioxan for 48 hours at 80°C, the yield was reduced to 66%.

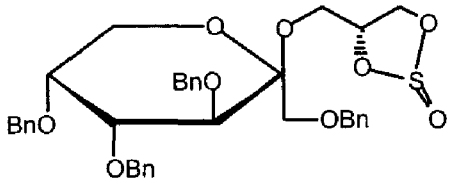
The above results were not unexpected. In the nucleophilic cleavage [6,13,34] of an oxirane ring the nucleophile becomes attached to one carbon atom and a hydroxyl group is then situated on the other. These groups have a *trans* relationship. In the reaction of a terminal oxirane, i.e. those that are derived from one primary and one secondary carbon atom, polar and steric effects combine to favour almost exclusive substitution at the terminal position. The stereochemistry of the hydroxyl group on the secondary carbon remains unaltered.[13,34]

5.2.2 ... *via* a cyclic sulfate intermediate

A solution of compound **2** in dichloromethane was treated with thionyl chloride in the presence of triethylamine as the base. The presumed cyclic sulfite **9** that had been formed, was not characterized but used directly in the subsequent oxidation step. It was, therefore, essential that all traces of triethylamine were removed, prior to this reaction.[12] Treatment of the crude product with sodium metaperiodate in the presence of ruthenium (III) chloride gave cyclic sulfate **10** in 71% yield as a syrup.

The product obtained was reacted with lithium azide in *N,N*-dimethylformamide for 1 hour at 70-80°C. A solution of the resultant compound **11** in tetrahydrofuran (THF), was treated

briefly with concentrated sulfuric acid to hydrolyze the intermediate mono-sulfate ester **11** to give the azide **4** in 77% yield. Since the nucleophilic ring-opening reaction of a cyclic sulfate can be rapid,[12,21] especially at the terminal position, the possibility of using THF as the solvent in a "one pot" sequence was investigated. It is known that lithium azide is much more soluble than the sodium salt in a range of organic solvents and its beneficial use in some displacement reactions has been reviewed.[33] Nucleophilic attack on the cyclic sulfate in THF using lithium azide was much slower (24 hr) than in *N,N*-dimethylformamide (1 hr) but subsequent hydrolysis, without the need for an intermediate work-up procedure, proceeded satisfactorily to give the azide **4** in reasonable yield (70%).



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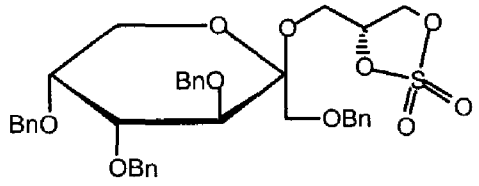

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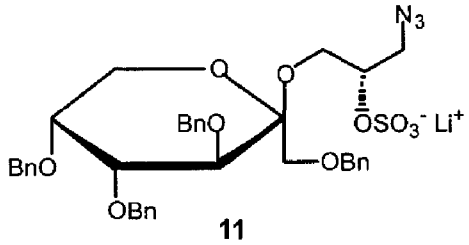

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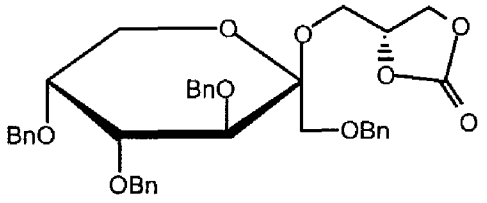
5.2.3 ... *via* a cyclic carbonate intermediate

Cyclic carbonates have also been used as a protecting function for diols in a variety of reactions,[37] especially in carbohydrate and nucleoside chemistry.[38-44] The various methods used for their syntheses have been comprehensively reviewed.[37] There are few reports on the nucleophilic reactions of these derivatives at their carbinol center, rather than on the carbonyl function.[45,46] The synthesis of a series of enantiopure amino alcohols *via* azido alcohol intermediates, which involved activation of the corresponding diols as cyclic carbonate derivatives, has been reported.[47] The cyclic esters were treated with sodium azide in *N,N*-dimethylformamide at various temperatures for various periods of time to give the corresponding azides in good yields. The presence of up to one equivalent of water in these reactions was found to be beneficial. Cyclic carbonates in which one of the parent hydroxyl groups was a secondary type, situated on a benzylic carbon, were found to be the most reactive.

Attempts were also made during this study to obtain the azido alcohol **4** *via* a cyclic carbonate intermediate. Treatment of the diol **2** with dimethyl carbonate in the presence of 1,8-diazabicyclo[5.4.0]undecene-7 (DBU) at 80°C for 12 hours gave the cyclic carbonate **12** in 77% yield as an oil. The product obtained was further characterized as the crystalline unprotected compound **13** by catalytic hydrogenolysis (H_2, Pd/C). Reaction of **12** with sodium azide in *N,N*-dimethylformamide containing one equivalent of water at 80-95°C was rather

sluggish and only 25% of the desired azide **4** was obtained after 7 days. Variation of the reaction conditions, *viz* temperature and water concentration, did not improve the rate of reaction, nor the yield of product **4**. The low yield of **4** could be attributed to decomposition of the carbonate **12** during the prolonged reaction times.

Despite the earlier recorded impressive results,[47] the use of cyclic carbonate esters as activating groups for the introduction of substituents on carbon atoms *via* nucleophilic attack cannot be seen as a general procedure.



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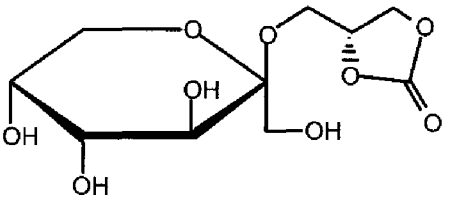

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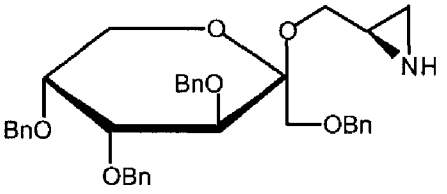


14

5.2.4 Reduction of *2(R)*-hydroxy-3-azidopropyl 1',3',4',5'-tetra-*O*-benzyl-β-D-fructopyranoside (4) with triphenylphosphine

The reduction of azides to primary amines constitutes a useful synthetic process for introduction of amino functions into many types of molecules.[31,33,48] A wide range of reagents including complex metallic hydrides, catalytic hydrogenation, sulfide-based systems and samarium iodide have been reported for this purpose.[49] Some of these methods are subject to interference or complications arising from other functional or protecting groups.

The use of triphenylphosphine as a mild reducing agent for azides has also been reported.[49,50] The azido derivative is converted initially into a phosphinimine, which is subsequently hydrolyzed to the amine.

$$RN_3 + Ph_3P \longrightarrow RN{=}PPh_3 \longrightarrow RNH_2$$

Several procedures have been described for the hydrolysis.[49-52] The procedure has been applied, *inter alia*, to carbohydrate [53] and nucleotide [54] derivatives.

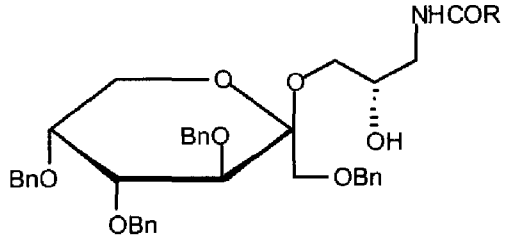
It was decided to use this reduction method for effecting the reduction of compound **4**, in view of the presence of the benzyl ether protecting groups. These are known [55] to be particularly prone to removal under the conditions of catalytic hydrogenation. Treatment of a vicinal azido alcohol derivative with triphenyphosphine can lead to either the reduced amino-alcohol, or to ring closure to give an aziridine.[56,57] This depends on the reaction conditions employed. These have been described in detail.[58-60]

Reaction of compound **4** with a solution of triphenyphosphine in pyridine, followed by hydrolysis with aqueous ammonium solution, yielded, after column chromatography pure amino alcohol **3** in 78% yield. Compound **3** was also the main product in attempts to obtain the aziridine **14** from the azide **4** using triphenylphosphine in various solvents. These reactions are described in more detail in Chapter 7.

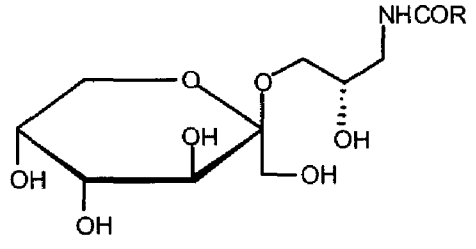
5.2.5 Acylation of *2(R)*-hydroxy-3-aminopropyl 1',3',4',5'-tetra-*O*-benzyl-β-D-fructopyranoside (3)

There is considerable current interest in carbohydrate-based amphiphiles as specialist surfactants.[61] Carbohydrates are relatively cheap, bio-degradable and possess a variety of functional groups capable of being substituted. Most of them have the capability of undergoing intermolecular hydrogen bonded interactions required for the stabilization of the various aggregates formed by these molecules (see Chapter 1). Some derivatives containing long-chain acyl amino groups are of particular interest for potential medicinal and pharmaceutical application.[4,5]

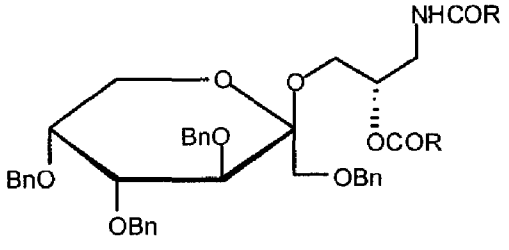
Controlled acylation of the amine **3** with long-chain aliphatic acid chlorides (C_{12}-C_{16}) yielded the corresponding amides **15**, **16**, and **17** (64-72%). Hydrogenolysis of compounds **15**, **16**, and **17** over palladized charcoal (10%) gave the fully deprotected mono amides **18**, **19**, and **20**.



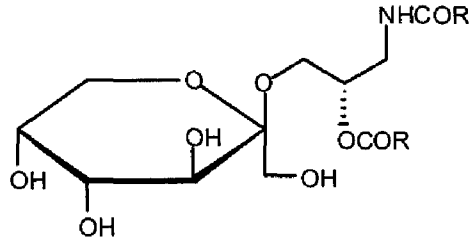
15 R =$C_{11}H_{23}$ (64%)
16 R =$C_{13}H_{27}$ (70%)
17 R =$C_{15}H_{31}$ (72%)



18 R =$C_{11}H_{23}$ (91.3%)
19 R =$C_{13}H_{27}$ (91.2%)
20 R =$C_{15}H_{31}$ (88.5%)



21 R =$C_{11}H_{23}$ (82%)
22 R =$C_{13}H_{27}$ (90%)
23 R =$C_{15}H_{31}$ (84%)



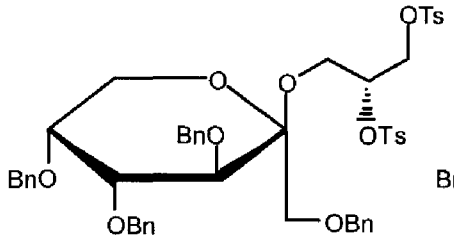
24 R =$C_{11}H_{23}$ (91.2%)
25 R =$C_{13}H_{27}$ (91.2%)
26 R =$C_{15}H_{31}$ (62%)

Acylation of the protected amides **15**, **16**, and **17** using the same acid chlorides gave the corresponding *O*-acyl derivatives **21**, **22**, and **23** in good yield (82-90%). Catalytic hydrogenolysis (Pd/C, 10%) in the same manner gave the debenzylated compounds **24**, **25**, and **26**. The yield of compound **26** (62%) was somewhat lower than the two other derivatives (91%),

due to the fact that it was a fairly low-melting compound (m.p. 51.5°C) and not easily purified. This route would also be amenable to the synthesis of mixed derivatives composed of differing acyl residues on the amide group and adjacent hydroxyl function. The preparation of these derivatives was not investigated during this study due to a shortage of time.

5.2.6 Synthesis of some *bis*-acylamino derivatives from *2(R)*,3-dihydroxypropyl 1',3',4',5'-tetra-*O*-benzyl-β-D-fructopyranoside [1-*O*-(1',3',4',5'-tetra-*O*-benzyl β-D-fructopyranosyl)-*sn*-glycerol]

It was then decided to extend the study by preparing some long-chain bis-acylamino compounds from the diol **2**. Treatment of compound **2** with an excess of *p*-toluenesulfonyl chloride in the usual manner gave the di-toluenesulfonate **27** in good yield (90%) as an oil. Treatment of **27** in *N,N*-dimethylformamide with sodium azide gave the bis-azido compound **28** (80%), which on reduction ($LiAlH_4$) yielded the di-amino derivative **29** (83%). Treatment of solutions of compound **29** in dichloromethane containing triethylamine with dodecanoyl, tetradecanoyl, and hexadecanoyl chlorides gave the corresponding long-chain diamides **30**, **31**, and **32** in good yield as oils. Catalytic hydrogenolysis (H_2, Pd/C) of **30**, **31**, and **32** in the usual manner then yielded the corresponding crystalline debenzylated derivatives **33**, **34**, and **35**.



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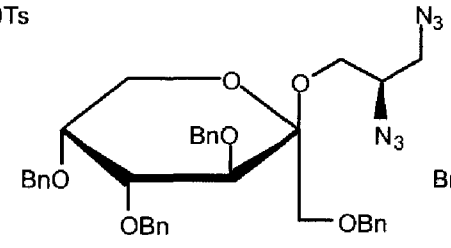

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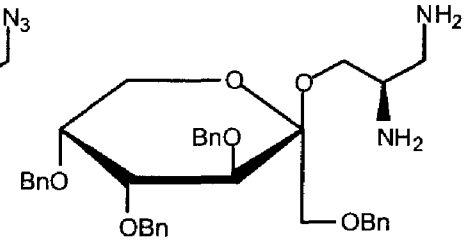

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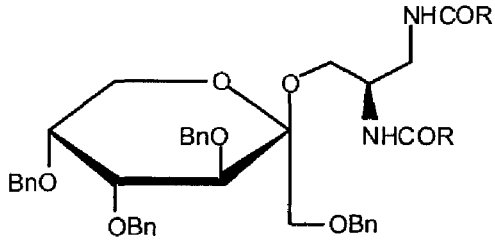
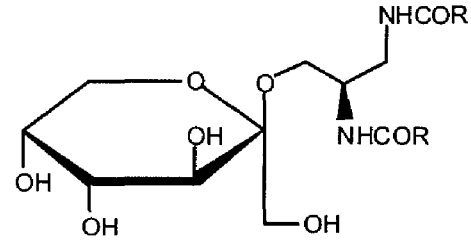


30 R = $C_{11}H_{23}$ (87.0 %)
31 R = $C_{13}H_{27}$ (81.3 %)
32 R = $C_{15}H_{31}$ (94.6 %)



33 R = $C_{11}H_{23}$ (71.2 %)
34 R = $C_{13}H_{27}$ (66.9 %)
35 R = $C_{15}H_{31}$ (65.2 %)

5.3 Concluding remarks

The results described in this chapter show that long-chain mono acyl amino and di-acyl amino compounds derived from the diol **2** are fairly readily available in moderate-to-good yields. Conversion of the diol **2** into the terminal azide **4** was achieved by nucleophilic attack by

azide ions on the oxirane **7**, prepared by two conventional routes, or on the cyclic sulfate **10**. Attempts to obtain compound **4** *via* a cyclic carbonate intermediate were not very successful. The azide **4** was reduced to the amine **3** using triphenylphosphine. This method was chosen to avoid any problem with the *O*-benzyl protecting groups. Treatment of the di-*O*-*p*-toluenesulfonate of **2** with azide ions followed by reduction ($LiAlH_4$) of the resultant bis-azide **28** gave the diamine **29** with inversion of configuration at C-2. Conventional acylation of **3** and **29** with long-chain acyl chlorides, followed by catalytic hydrogenation (de-benzylation) gave the desired amides in acceptable overall yields.

5.4 Experimental section

For general experimental procedures see Chapter 3.

2(S)-O-Acetyl-3-chloropropyl 1',3',4',5'-tetra-O-benzyl β-D-fructopyranoside (5)

Trimethylsilyl chloride (0.625 mL, 4.9 mmol, 2.5 eq) was added to a stirred, cooled (0°C) solution of the diol **2** (1.2 g, 1.95 mmol) in dichloromethane (10 mL) containing triethyl orthoacetate (0.49 mL, 3.9 mmol, 2.0 eq). The reaction mixture was stirred for 1 hr, concentrated *in vacuo* and the resultant material purified by column chromatography (n-hexane-ethylacetate, 3:1) to yield compound **5** (1.1654 g, 86.7%) as a pure colourless oil. $[\alpha]_D$ – 47.40176° ($CHCl_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 169.7 (*C*=O), 138.9, 138.4, 138.3, 137.8, 128.1, 127.9, 127.6, 127.5, 127.4, 127.0, (aromatic-C), 101.5 (C-2), 78.5 (C-3), 76.7 (C-4), 75.6, 74.7 (benzylic-C), 73.5 (C-5), 72.0, 71.4 (benzylic-C), 71.1 (C-1), 70.0 (C-1'), 61.3 (C-6), 59.7 (C-2'), 42.6 (C-3') and 20.7 ($COCH_3$) ppm. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.40-7.22 (m, 20H, aromatic H), 5.15-4.93 (dd, 1H, J = 5.2 Hz, H-2'), 4.91, 4.62 (2d, 2H, J = 11.4 Hz, benzylic-H), 4.76, 4.71 (2d, 2H, J = 12.6 Hz, benzylic-H), 4.66, 4.45 (2d, 2H, J = 11.8 Hz, benzylic-H), 4.61, 4.59 (2d, 2H, J = 11.7 Hz, benzylic-H), 4.32 (d, 1H, J = 10.0 Hz, H-3), 3.92 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.1 Hz, H-4), 3.89 (dd, 1H, $J_{5,6eq}$ = 2.0 Hz, $J_{6ax,6eq}$ = 12.3 Hz, H-6eq), 3.86 (dd, 1H, $J_{5,6ax}$ = 1.9 Hz, $J_{6ax,6eq}$ = 12.3 Hz, H-6ax), 3.79 (m, 1H, H-5), 3.76 (2d, 1H, J = -10.2 Hz, H-1a), 3.68 (d, 1H, $J_{3'a,2'}$ = 6.2 Hz, H-3'a), 3.65 (d, 1H, $J_{3'b,2'}$ = 6.2 Hz, H-3'b), 3.65 (2d, 1H, J = -10.2 Hz, H-1b), 3.62 (dd, 1H, J = 5.1 Hz, H-1'a), 3.60 (dd, 1H, J = 5.1 Hz, H-1'b), 2.0 (s, 3H, OCH_3) ppm.

2(S)-O- Acetyl-3-chloropropyl β-D-fructopyranoside (6)

A solution of compound **5** (230 mg, 0.340 mmol) in methanol (30 mL) was subjected to hydrogenolysis in the presence of palladium on charcoal (10%, 60 mg) for 2 hr. The catalyst was removed by filtration, washed with methanol, and the combined filtrate and washings concentrated *in vacuo* to yield compound **6** as white crystals (78 mg, 72.6%). A sample of the product was crystallized (ether / ethanol) to give pure **6**, m.p. 149-150°C; $[\alpha]_D$ –52.3° (DMF); MS (CI-CH_4) M/z 315 (M^++H), 163 (M^++H –$C_5H_9O_3Cl$). ^{13}C-NMR (D_2O, 75 MHz) δ 174.58 (*C*=O), 102.01 (C-2), 73.67 (C-2'), 70.74, 70.31, 69.42 (C-3, C-4, C-5), 65.28 (C-1'), 62.51 (C-1), 61.07 (C-6), and 43.87 (C-3') ppm. ^{1}H-NMR (D_2O, 400 MHz) δ 5.20-5.14 (m, 1H, H-2'), 3.95 (dd, 1H, H-3'a), 3.88-3.70 (m, 9H, H-1', H-1, H-3, H-4, H-5, H-6), and 3.68 (dd, 1H, H-3'b) ppm. *Anal* calc for $C_{11}H_{19}ClO_8$: C 41.98; H 6.09. Found: C 41.68; H 6.07%.

*2(**R**),3-Oxiranylpropyl 1',3',4',5'-tetra-O-benzyl* β-**D**-*fructopyranoside (7)*

Method A [19]

A stirred, cooled (0°C) solution of compound **5** (4.0 g, 6.5 mmol) in dichloromethane (10 mL) was treated with 1**M** sodium methoxide in methanol (1 mL) in two portions and set aside at room temperature for 12 hr. The mixture was treated with more dichloromethane (50 mL), washed with water (2x25 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography of the residue (n-hexane-ethyl acetate 2:1) yielded **7** (3.6 g, 92.6%) as a colourless oil. $[\alpha]_D$ –50.3° ($CHCl_3$); MS (CI-CH_4) M/z 597 (M^++H), 523 (M^++H –$C_3H_6O_2$), 475 (M^++H –H_2COBn) ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 138.77, 138.55, 138.47, 137.96, 128.25, 128.13, 128.09, 127.74, 127.63, 127.45, 127.32 (aromatic-C), 101.47 (C-2), 78.56 (C-3), 76.10 (C-4), 75.47, 73.53 (benzylic-C), 73.50 (C-5), 72.07, 71.16 (benzylic-C), 70.34 (C-1'), 61.05 (C-1), 60.74 (C-6), 50.9 (C-2') and 44.7 (C-3') ppm. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.40-7.20 (m, 20H, aromatic H), 4.91, 4.65 (2d, 2H, J = 11.2 Hz, benzylic-H), 4.76, 4.70 (2d, 2H, J = 12.6 Hz, benzylic-H), 4.63, 4.42 (2d, 2H, J = 11.8 Hz, benzylic-H), 4.62, 4.60 (2d, 2H, J = 10.8 Hz, benzylic-H), 4.33 (d, 1H, J = 10.1 Hz, H-3), 3.93 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.1 Hz, H-4), 3.85 (dd, 1H, $J_{5,6eq}$ = 2.2 Hz, $J_{6ax,6eq}$ = -12.3 Hz, H-6eq), 3.82 (dd, 1H, $J_{5,6ax}$ = 1.9 Hz, $J_{6ax,6eq}$ = -12.3 Hz, H-6ax), 3.79 (m, 1H, H-5), 3.75 (2d, 1H, J = -10.2 Hz, H-1a), 3.65 (2d, 1H, J = -10.2 Hz, H-1b), 2.70 (m, 1H, H-2'), 2.67 (d, 1H, $J_{3'a,2'}$ = 2.7 Hz, H-3'a), 2.65 (d,1H, $J_{3'b,2'}$ = 2.7 Hz, H-3'b) ppm.

Method B [19]

A solution of **5** (297 mg, 0.43 mmol) in methanol (5 mL) was treated with potassium carbonate (118.7 mg, 0.86 mmol, 2 eq). The suspension was stirred vigorously at room temperature for 6 hr, filtered, and the inorganic residue was washed with dichloromethane. The combined filtrate and washings were concentrated *in vacuo* and the resultant residue purified by column chromatography (n-hexane-ethyl acetate, 2:1) to give **7** (176 mg, 68%) as a pure colourless oil. $[\alpha]_D$ –50.2° ($CHCl_3$); The spectral characteristics were identical to those described above.

Method C

A stirred cooled (0°C) solution of compound **2** (481 mg, 0.783 mmol) in dry pyridine (5 mL) was treated with *p*-toluenesulfonyl chloride (149 mg, 0.783 mmol, 1.0 eq) and set aside at room temperature for 24 hr. The reaction mixture was poured in ice water and left for 1 hr, diluted with dichloromethane (50 mL) and washed successively with aqueous hydrochloric acid (2**M**, 20 mL), water (20 mL) and saturated aqueous sodium hydrogen carbonate (20 mL). The organic extract was dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (n-hexane-ethyl acetate, 3:2) of the crude material gave **8** (473 g, 79%) as a pure colourless oil. $[\alpha]_D$ –48.0° ($CHCl_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 138.06, 138.92, 138.40, 137.67, 129.75, 128.19, 128.09, 127.78, 127.66, 127.73, 127.69, 127.60, 127.47, 127.29 (aromatic-C), 101.65 (C-2), 78.30 (C-3), 76.47 (C-4), 76.16, 75.25 (benzylic-C), 73.64 (C-5), 73.70 (C-2'), 72.00, 71.20 (benzylic-C), 70.23 (C-1'), 64.73 (C-1), 61.36 (C-6), 50.81 (C-3'), and 21.61, 15.43 (CH_3) ppm. ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 7.79-7.15 (m, 24H, aromatic H), 4.90 (d, 1H, J = 11.2 Hz,

benzylic-H), 4.75, 4.69 (2d, 2H, J = 12.6 Hz, benzylic-H), 4.66-4.42 (m, 5H, benzylic-H), 4.27-3.78 (m, 2H, H-3, H-4), 3.79-3.30 (m, 10H, H-1a, H-1b, H-1'a, H-1'b, H-2', H-3', H-5, H-6eq, H-6ax), 2.39 (s, 3H, C*H*$_3$).ppm.

A stirred solution of compound **8** (245 mg, 0.319 mmol) in methanol (5 mL) was treated with sodium methoxide (1M, 6 mL) at room temperature for 2 hr. The mixture was treated with water (20 mL) and dichloromethane (20 mL) and the separated organic layer was washed with water (10 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (n-hexane-ethyl acetate, 1:1) to give **7** [154 mg, 33% (overall yield)] as a pure colourless oil. $[\alpha]_D$ –50.2° ($CHCl_3$); The spectral characteristics were identical to those described above.

*2(**R**),3-Dihydroxypropyl 1',3',4',5'-tetra-*O*-benzyl* β-D-*fructopyranoside 2,3-*O*-cyclic sulfate (**10**)*

A stirred, cooled (0°C) solution of compound (**2**) (1.0 g, 1.63 mmol) in dichloromethane (5 mL) containing triethylamine (0.6 mL) was treated dropwise with a solution of thionyl chloride (0.15 mL, 1.8 mmol) in dichloromethane (3 mL) over 10 mins, and then set aside for a further10 mins. The mixture was diluted with dichloromethane (50 mL), washed with water (2x25 mL), and the organic layer dried ($MgSO_4$) and concentrated *in vacuo*. The resultant crude material dissolved in a mixture of CCl_4 / CH_3CN / H_2O (1:1:1, 15 mL) was treated with sodium metaperiodate (484 mg, 2.26 mmol, 1.39 eq) and $RuCl_3.xH_2O$ (2 mg, 0.01 mmol) at room temperature for 1 hr. The mixture was then diluted with ether (40 mL), and the organic layer washed with water (2x10 mL), saturated aqueous $NaHCO_3$ (2x10 mL), sodium chloride solution (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (ethyl acetate-n-hexane, 1:1) of the residue gave the cyclic sulfate **10** as a syrup (780 mg, 71%). $[\alpha]_D$ –43.7° ($CHCl_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 138.86, 138.34, 138.29, 128.31, 128.25, 128.14, 128.09, 127.95, 127.79, 127.75, 127.66, 127.59, 127.54, 127.31 (aromatic-C), 101.50 (C-2), 78.71 (C-3), 77.86 (C-4), 76.31 (C-5), 75.6, 75.06, 73.69 (benzylic-C), 73.47 (C-2'), 72.07 (benzylic-C), 70.45 (C-1'), 68.33 (C-1), 61.43 (C-6), 60.07 (C-3').ppm. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.40-7.24 (m, 20H, aromatic H), 5.04, 4.61 (2d, 2H, J = 11.3 Hz, benzylic-H), 4.97, 4.83 (2d, 2H, J = 12.6 Hz, benzylic-H), 4.58, 4.37 (2d, 2H, J = 11.9 Hz, benzylic-H), 4.26 (d, 1H, J = 10.0 Hz, H-3), 3.85 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.2 Hz, H-4), 3.83 (m, 1H, H-5), 3.74 (dd, 1H, J = 4.4 Hz, H-1'a), 3.72 (dd, 1H, J = 4.4 Hz, H-1'b), 3.61 (2d, 1H, J = -10.2 Hz, H-1a), 3.55 (2d, 1H, J = -10.2 Hz, H-1b), 3.50 (d, 1H, $J_{3'a,2}$ = 7.0 Hz, H-3'a), 3.45 (d, 1H, $J_{3'b,2}$ = 7.0 Hz, H-3'b) ppm.

*2(**R**)-Hydroxy-3-azidopropyl 1',3',4',5'-tetra-*O*-benzyl* β-D-*fructopyranoside (**4**)*

Method A [62](*via* cyclic sulfate **10**).

A stirred solution of the cyclic sulfate **10** (480 mg, 0.71 mmol) in DMF (5 mL) was treated with lithium azide (63.9 mg, 1.42 mmol, 2.0 eq) and heated at 80°C for 1 hr. The mixture was concentrated *in vacuo*, dissolved in freshly distilled THF (10 mL), cooled (0°C), and few drops of conc H_2SO_4 was added, and the mixture was set aside at room temperature for 15 mins. The reaction was then complete (TLC) and saturated aqueous sodium hydrogen carbonate (10 mL) was added, stirred for an extra 15 mins to neutralize the acid, and then treated with ether

(20 mL). The separated organic layer was washed with 10% NaCl solution (20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Column chromatography (n-hexane-ethyl acetate, 1:1) of the residue gave compound **4** as a colourless oil (348 mg, 76.9%). $[\alpha]_D$ –42.3° ($CHCl_3$); MS (CI-CH_4) M/z 640 (M^++H), 523 (M^++H -$HOCH_2CH(OH)CH_2N_3$). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 138.39, 138.37, 138.31, 137.64, 128.28, 128.20, 128.09, 128.06, 127.9, 127.7, 127.6, 127.5, 127.4 (aromatic-C), 101.35(C-2), 78.5 (C-3), 77.3 (C-4), 75.6, 73.65 (benzylic-C), 73.20 (C-5), 71.99, 71.25 (benzylic-C), 70.12 (C-1), 69.63 (C-2'), 63.35 (C-1'), 61.2 (C-6), 53.0 (C-3') ppm. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.40-7.19 (m, 20H, aromatic H), 4.88, 4.60 (2d, 2H, J = 10.8 Hz, benzylic-H), 4.75, 4.70 (2d, 2H, J = 12.6 Hz, benzylic-H), 4.65, 4.45 (2d, 2H, J = 11.8 Hz, benzylic-H), 4.61, 4.58 (2d, 2H, J = 11.0 Hz, benzylic-H), 4.31 (d, 1H, J = 10.0 Hz, H-3), 3.92 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.2 Hz, H-4), 3.88 (dd, 1H, $J_{5,6eq}$ = 2.0 Hz, $J_{6ax,6eq}$ = -12.3 Hz, H-6eq), 3.85 (dd, 1H, $J_{5,6ax}$ = 1.9 Hz, $J_{6ax,6eq}$ = -12.3 Hz, H-6ax), 3.81 (m, 1H, H-2'), 3.79 (m, 1H, H-5), 3.77 (2d, 1H, J = -10.2, H-1a), 3.64 (2d, 1H, J = -10.2 Hz, H-1b), 3.49 (dd, 1H, J = 7.3 Hz, H-1'a), 3.46 (dd, 1H, J = 7.3 Hz, H-1'b), 3.25 (d, 1H, $J_{3'a,2'}$ = 3.6 Hz, H-3'a), 3.24 (d, 1H, $J_{3'b,2'}$ = 3.6 Hz, H-3'b), 2.0 (bs, 1H, O*H*) ppm.

Method B [36] (*via* oxirane **7**).

A stirred solution of the oxirane **7** (667 mg, 1.12 mmol) in a mixture of 2-methoxyethanol / water (20 mL, 3:1) was treated with sodium azide (291.2 mg, 4.48 mmol, 4.0 eq) and ammonium sulfate (591 mg, 4.48 mmol, 4.0 eq), and then set aside at room temperature for 4 days. The mixture was treated with water (20 mL) and ether (50 mL), and the separated aqueous layer extracted with ether (2x25 mL). The combined organic layer was washed with 10% sodium chloride solution (20 mL)), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (n-hexane-ethyl acetate, 2:1) of the crude material gave compound **4** (673 mg, 94%) as a pure colourless oil. $[\alpha]_D$ – 42.2° ($CHCl_3$); The spectral data for the product were as reported above.

Method C [47] (*via* cyclic carbonate **12**).

A stirred solution of the diol **2** (319 mg, 0.5 mmol) in dimethyl carbonate (15 mL) was treated with DBU (0.2 mL, 1.5 mmol, 3 eq) and heated at 80°C for 12 hr. Concentration of the reaction mixture *in vacuo*, followed by column chromatography (n-hexane-ethyl acetate, 1:1) of the residue gave **12** (245 mg, 77%) as a colourless oil. $[\alpha]_D$ –54.5° ($CHCl_3$).^{13}C-NMR ($CDCl_3$, 75 MHz) δ 154.93 (*C*=O), 139.14, 138.51, 138.46, 137.80, 128.30, 128.25, 128.18, 128.05, 128.02, 127.83, 127.77, 127.73,127.67, 127.61, 127.48, 127.43, 127.16 (aromatic-C), 101.45 (C-2), 78.56 (C-3), 76.33 (C-4), 75.48, 73.71 (benzylic-C), 73.36 (C-5), 71.51, 71.45 (benzylic-C), 70.48 (C-1), 65.88 (C-2'), 62.57 (C-1'), 61.55 (C-6), and 60.78 (C-3') ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.37-7.20 (m, 20H, aromatic H), 4.92 (1d, 1H, J = 11.5 Hz, benzylic-H), 4.79-4.74 (m, 1H, H-2'), 4.70 (m, 2H, benzylic-H), 4.64-4.55 (m, 3H, benzylic-H), 4.50-4.45 (m, 2H, benzylic-H), 4.23 (d, 1H, J = 10.1 Hz, H-3), 3.97 (dd, 1H, $J_{3,4}$, $J_{4,5}$ =3.1 Hz, H-4), 3.89-3.84 (m, 2H, H-1'), 3.83 (dd, 1H, $J_{5,6eq}$ = 1.78 Hz, $J_{6ax,6eq}$ = -12.3 Hz, H-6eq), 3.80 (dd, 1H, $J_{5,6ax}$ = 1.77 Hz, $J_{6ax,6eq}$ = -12.3 Hz, H-6ax), 3.71 (d, 1H, J = -10.2 Hz, H-1a), 3.63 (d, 1H, J = -10.2 Hz, H-1b), 3.58 (d, 1H, $J_{3'a,2'}$ = 2.36 Hz, H-3'a), 3.55 (d, 1H, $J_{3'b,2'}$ = 2.36 Hz, H-3'b) ppm.

A stirred solution of cyclic carbonate **12** (170 mg, 0.27 mmol) in a mixture of DMF (10 mL) and water (4.8 mL, 0.27 mmol) was treated with sodium azide (86.3 mg, 1.38 mmol, 5 eq) and heated at 80 C for seven days. The mixture was treated with water (20 mL) and ether (50 mL) and the separated organic layer was washed with 10% sodium chloride solution (20 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (n-hexane-ethyl acetate, 2:1) to give azido alcohol **4** (41 mg, 24%) as a pure colourless oil. $[\alpha]_D$ –42.0° ($CHCl_3$).

*2(**R**),3-Dihydroxypropyl* β-**D**-*fructopyranoside 2,3-*O*-cyclic carbonate (13)*

Compound **12** (278 mg, 0.434 mmol) in methanol (30 mL) was treated with palladium on charcoal (10%, 60 mg) and hydrogenolysed for 1 hr. The catalyst was removed by filtration, washed with methanol, and the combined filtrate and washings concentrated *in vacuo* to yield compound **13** as a white crystals (80 mg, 65.8%). A sample of the product was crystallized from a mixture of ether / ethanol, m.p 143-144°C: $[\alpha]_D$ –47.4° ($CHCl_3$); MS (CI-CH_4) M/z 281 (M^++H), 163 (M^++H –$C_4H_6O_4$). ^{13}C-NMR [$CDCl_3$ + CD_3OD, 75 MHz] δ 155.69 (*C*=O), 99.58 (C-2), 75.04 (C-2'), 69.88, 69.39, 68.91 (C-3, C-4, C-5), 65.96 (C-1'), 63.57 (C-3'), 62.80 (C-1), and 60.03 (C-6) ppm. ^{1}H-NMR [$CDCl_3$ + CD_3OD, 400 MHz] δ 4.97-4.93 (m, 1H, H-2'), 4.68 (dd, 1H, $J_{1'a,2'}$ = 5.0 Hz, H-1'a), 4.55 (dd, 1H, $J_{1'b,2'}$ = 5.0 Hz, H-1'b), 3.95 (dd, 1H, $J_{3'a,2'}$ = 2.32 Hz, H-3'a), 3.90-3.17 (m, 7H, H-1, H-3, H-4, H-5, H-6), and 3.68 (dd, 1H, $J_{3'b,2'}$ = 2.0 Hz, H-3'b) ppm. *Anal* calc for $C_{10}H_{16}O_9$: C 42.86; H 5.75. Found: C 42.80; H 5.67%.

*2(**R**)-Hydroxy-3-aminopropyl 1',3',4',5'-tetra-*O*-benzyl* β-**D**-*fructopyranoside (3)*

A stirred solution of compound **4** (1.19 g, 1.86 mmol) in pyridine (10 mL) was treated with triphenylphosphine (975.72 mg, 3.72 mmol, 2.0 eq) at room temperature until evolution of nitrogen ceased. Aqueous ammonia solution (25%, 2 mL) was then added and stirring was continued for a further 12 hr. The mixture was concentrated *in vacuo* and column chromatography of the residue (CH_2Cl_2 - MeOH, 9:1) gave **3** (895 mg, 79%) as a pure colourless oil. $[\alpha]_D$ –52.0° ($CHCl_3$); MS (CI-CH_4) M/z 614 (M^++H), 536 (M^+ +H -C_6H_6), 523 (M^+ +H -$HOCH_2CH(OH)CH_2NH_2$), 492 (M^+ +H -CH_2OBn). ^{13}C -NMR ($CDCl_3$, 75 MHz) δ 138.62, 138.50, 138.39, 137.82, 128.28, 128.18, 127.98, 127.87, 127.73, 127.65, 127.58, 127.48 (aromatic-C), 102.21 (C-2), 78.59 (C-3), 77.31 (C-4), 75.51, 73.62 (benzylic-C), 73.35 (C-5), 71.95, 71.19 (benzylic-C), 70.33 (C-1), 70.18 (C-2'), 64.53 (C-1'), 61.10 (C-6) and 44.11 (C-3') ppm. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.40-7.19 (m, 20H, aromatic H), 4.90, 4.60 (2d, 2H, J = 10.8 Hz, benzylic-H), 4.75, 4.70 (2d, 2H, J = 12.5 Hz, benzylic-H), 4.68, 4.45 (2d, 2H, J = 11.8 Hz, benzylic-H), 4.60, 4.58 (2d, 2H, J = 10.3 Hz, benzylic-H), 4.33 (d, 1H, J = 10.0 Hz, H-3), 3.94 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.2 Hz, H-4), 3.87 (dd, 1H, $J_{5,6eq}$ = 1.6 Hz, $J_{6ax,6eq}$ = -12.3 Hz, H-6eq), 3.84 (dd, 1H, $J_{5,6ax}$ = 1.5 Hz, $J_{6ax,6eq}$ = -12.3 Hz, H-6ax), 3.78 (m, 1H, H-2'), 3.77 (2d, 1H, J = -10.2 Hz, H-1a), 3.63 (2d, 1H, J = -10.2 Hz, H-1b), 3.66 (m, 1H, H-5), 3.52 (dd, 1H, J = 6.1 Hz, H-1'a), 3.35 (dd, 1H, J = 6.1 Hz, H-1'b), 2.67 (d, 1H, $J_{3'a,2}$ = 4.3 Hz, H-3'a), 2.59 (d, 1H, $J_{3'b,2}$ = 4.3 Hz, H-3'b), 2.4 (bs, 1H, O*H*) ppm.

*2(**R**)-Hydroxy-3-dodecanoylamidopropyl 1',3',4',5'-tetra-*O*-benzyl* β-**D**-*fructopyranoside (15)*

A stirred, cooled (0°C) solution of compound **3** (1.0286 g, 1.7 mmol) in dichloromethane (10 mL) and triethylamine (0.6 mL) was treated with lauroyl chloride (0.4 mL, 1.87 mmol, 1.1

eq) and set aside for 1 hr. The mixture was diluted with dichloromethane (50 mL) and washed, successively with aqueous hydrochloric acid (2M, 50 mL), water (50 mL) and a solution of saturated sodium hydrogen carbonate (50 mL). The organic extract was dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (n-hexane-ethyl acetate, 3:1) of the crude material gave **15** (867 mg, 64%) as a pure colourless oil. $[\alpha]_D$ –53.8° ($CHCl_3$). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 174.30 (*C*=O), 138.39, 138.29, 137.68, 128.42, 128.31, 128.22, 128.17, 127.90, 127.74, 127.65, 127.55 (aromatic-C), 101.05 (C-2), 78.89 (C-3), 77.32 (C-4), 75.73, 73.71 (benzylic-C), 73.14 (C-5), 71.97, 71.21 (benzylic-C), 70.27 (C-1), 69.25 (C-2'), 64.41 (C-1'), 61.09 (C-6), 42.29 (C-3'), 36.46 ($COCH_2$), 31.87 ($COCH_2CH_2$), 29.58-22.65 (aliphatic C), and 14.08 (CH_3) ppm. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.39-7.18 (m, 20H, aromatic H), 6.23 (t, 1H, J = 6.5 Hz N*H*CO), 4.90, 4.62 (2d, 2H, J = 10.7 Hz, benzylic-H), 4.76, 4.69 (2d, 2H, J = 12.5 Hz, benzylic-H), 4.67, 4.45 (2d, 2H, J = 11.8 Hz, benzylic-H), 4.61, 4.58 (2d, 2H, J = 12.2 Hz, benzylic-H), 4.32 (d, 1H, J = 9.9 Hz, H-3), 3.90 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.2 Hz, H-4), 3.87 (dd, 1H, $J_{5,6eq}$ = 1.6 Hz, $J_{6ax,6eq}$ = -12.3 Hz, H-6eq), 3.84 (dd, 1H, $J_{5,6ax}$ = 1.5 Hz, $J_{6ax,6eq}$ = -12.3 Hz, H-6ax), 3.80 (m, 1H, 5), 3.77 (m, 1H, H-2'), 3.75 (2d, 1H, J = -10.2 Hz, H-1a), 3.65 (2d, 1H, J = -10.2 Hz, H-1b), 3.43 (dd, 1H, $J_{3'a,2'}$ = 6.2 Hz, H-3'a), 3.41 (dd, 1H, $J_{3'b,2'}$ = 6.2 Hz, H-3'b), 2.26 (bs, 1H, O*H*), 1.50 (m, 2H, CH_2CH_3), 1.29 (m, 18H, aliphatic H), and 0.87 (t, 3H, CH_3) ppm.

*2(**R**)-Hydroxy-3-tetradecanoylamidopropyl 1',3',4',5'-tetra-*O*-benzyl β-**D**-fructopyranoside (16)*

Compound **16** (380 mg) was synthesized by the same procedure used to obtain compound **15** but using tetradecanoyl chloride. Column chromatography (n-hexane-ethyl acetate, 3:1) of the crude material gave **16** (380 mg, 70%) as a pure colourless oil. $[\alpha]_D$ –49.2° ($CHCl_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 174.28 (*C*=O), 138.62, 138.47, 138.40, 137.76, 128.31, 128.22, 128.07, 127.90, 127.74, 127.60, 127.55 (aromatic-C), 101.11 (C-2), 79.03 (C-3), 77.42 (C-4), 75.66, 73.76 (benzylic-C), 73.36 (C-5), 72.06, 71.32 (benzylic-C), 70.44 (C-1), 69.37 (C-2'), 64.47 (C-1'), 61.22 (C-6), 42.44 (C-3'), 36.46 ($COCH_2$), 31.89 ($COCH_2CH_2$), 29.62-22.65 (aliphatic C), and 14.07 (CH_3) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.39-7.19 (m, 20H, aromatic H), 6.18 (t, 1H, J = 6.5 Hz N*H*CO), 4.88, 4.61 (2d, 2H, J = 10.8 Hz, benzylic-H), 4.75, 4.69 (2d, 2H, J = 12.5 Hz, benzylic-H), 4.67, 4.46 (2d, 2H, J = 11.8 Hz, benzylic-H), 4.30 (d, 1H, J = 9.9 Hz, H-3), 3.91 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.1 Hz, H-4), 3.89 (dd, 1H, $J_{5,6eq}$ = 1.6 Hz, $J_{6ax,6eq}$ = -12.3 Hz, H-6eq), 3.84 (dd, 1H, $J_{5,6ax}$ = 1.5 Hz, $J_{6ax,6eq}$ = -12.3 Hz, H-6ax), 3.80 (m, 1H, H-5), 3.68-3.51 (m, 3H, H-2', H-1a, H-1b), 3.47 (dd, 1H, $J_{3'a,2'}$ = 5.8 Hz, H-3'a), 3.43 (dd, 1H, $J_{3'b,2'}$ = 5.8 Hz, H-3'b), 2.0-1.93 (m, 2H, $COCH_2CH_2$), 1.50 (m, 2H, CH_2CH_3), 1.30 (m, 20H, aliphatic H), and 0.88 (t, 3H, CH_3) ppm.

*2(**R**)-Hydroxy-3-hexadecanoylamidopropyl 1',3',4',5'-tetra-*O*-benzyl β-**D**-fructopyranoside (17)*

Compound **17** (598 mg) was prepared by the same procedure used to prepare compound **15** but using hexadecanoyl chloride. Column chromatography (n-hexane-ethyl acetate, 3:1) of the crude product gave **17** (598 mg, 72%) as a pure colourless oil. $[\alpha]_D$ –55.3° ($CHCl_3$). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 174.26 (*C*=O), 138.60, 138.44, 138.39, 137.75, 128.30, 128.21, 128.08, 127.92, 127.73, 127.61, 127.54 (aromatic-C), 101.09 (C-2), 79.04 (C-3), 77.43 (C-4),

75.65, 73.74 (benzylic-C), 73.33 (C-5), 72.07, 71.31 (benzylic-C), 70.43 (C-1), 69.36 (C-2'), 64.48 (C-1'), 61.21 (C-6), 42.42 (C-3'), 36.46 ($COCH_2$), 31.88 ($COCH_2CH_2$), 29.66-22.61 (aliphatic C), and 14.07 (CH_3) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.39-7.19 (m, 20H, aromatic H), 6.17 (t, 1H, J = 6.5 Hz N*H*CO), 4.86, 4.63 (2d, 2H, J = 10.8 Hz, benzylic-H), 4.76, 4.68 (2d, 2H, J = 12.5 Hz, benzylic-H), 4.67, 4.45 (2d, 2H, J = 11.8 Hz, benzylic-H), 4.30 (d, 1H, J = 9.9 Hz, H-3), 3.91 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.1 Hz, H-4), 3.89 (dd, 1H, $J_{5,\ 6eq}$ = 1.6 Hz, $J_{6ax,\ 6eq}$ = -12.3 Hz, H-6eq), 3.84 (dd, 1H, $J_{5,\ 6ax}$ = 1.5 Hz, $J_{6ax,\ 6eq}$ = -12.3 Hz, H-6ax), 3.81 (m, 1H, H-5), 3.68-3.51 (m, 3H, H-2', H-1a, H-1b), 3.47 (dd, 1H, $J_{3'a,\ 2'}$ = 5.8 Hz, H-3'a), 3.43 (dd, 1H, $J_{3'b,\ 2'}$ = 5.8 Hz, H-3'b), 2.0-1.93 (m, 2H, $COCH_2CH_2$), 1.50 (m, 2H, CH_2CH_3), 1.30 (m, 24H, aliphatic H), and 0.88 (t, 3H, CH_3) ppm.

*2(**R**)-Hydroxy-3-dodecanoylamidopropyl* β-**D**-*fructopyranoside (**18**)*

A solution of compound **15** (406 mg, 0.51 mmol) in methanol (30 mL) was subjected to hydrogenolysis in the presence of palladium on charcoal (10%, 100 mg) for 2 hr. The catalyst was removed by filtration, washed with methanol and the combined filtrate and washings concentrated *in vacuo* to yield compound **18** as white crystals (203 mg, 91.3%). A sample of the product was crystallized (ether / ethanol) to give pure **18**. m.p. 118-120°C: $[\alpha]_D$ –66.5° (DMF); MS (FAB-Na^+) M/z 458.3 (M^++ Na^+), 274 (M^++ Na^+-$HCOC_{11}H_{23}$), 256 (M^++ Na^+-$C_6H_{11}O_6$). ^{13}C-NMR [$CDCl_3$ + CD_3OD, 75 MHz] δ 174.84 (*C*=O), 99.84 (C-2), 69.99, 69.88, 69.27, 69.16 (C-3, C-4, C-5, C-2'), 63.76 (C-1), 62.97 (C-1'), 62.39 (C-6), 41.57 (C-3'), 36.30 (-$COCH_2$), 31.71-22.48 (aliphatic C) and 13.86 (CH_3) ppm. ^{1}H-NMR [$CDCl_3$ + CD_3OD, 400 MHz] δ 6.95 (t, 1H, N*H*CO), 3.93-3.68 (m, 8H, H-1, H-2', H-3, H-4, H-5, H-6), 3.51-3.37 (m, 3H, H-1'a, H-1'b, H-3'b), 3.19 (dd, 1H, J = 6.8 Hz, H-3'a), 2.19 (t, 2H, $CH_2NC(O)$), 1.60 (m, 2H, CH_2CH_3), 1.30-1.26 (m, 16H, aliphatic H), and 0.88 (t, 3H, J = 6.8 Hz, CH_3) ppm. *Anal* calc for $C_{21}H_{41}NO_8$: C 57.91; H 9.49; N 3.22. Found: C 57.36; H 9.62; N 3.10%.

*2(**R**)-Hydroxy-3-tetradecanoylamidopropyl* β-**D**-*fructopyranoside (**19**)*

Hydrogenolysis of compound **16** (354 mg, 0.430 mmol) in the above described manner gave **19** (180 mg, 91.2%) as white crystals. A sample of the product was crystallized (ether / ethanol) to give pure **19**. m.p. 104-5°C: $[\alpha]_D$ –64.1° (DMF); MS (FAB-Na^+) M/z 486.3 (M^++ Na^+), 303 (M^++ Na^+-$C_{13}H_{27}$), 285 (M^++ Na^+-$C_{13}H_{27}$, -H_2O). ^{13}C-NMR [$CDCl_3$ + CD_3OD, 75 MHz] δ 174.84 (*C*=O), 99.78 (C-2), 69.90, 69.83, 69.23, 69.11 (C-3, C-4, C-5, C-2'), 63.71 (C-1), 62.91 (C-1'), 62.31 (C-6), 41.52 (C-3'), 36.22 (-$COCH_2$), 31.67-22.43 (aliphatic C) and 13.78 (CH_3) ppm. ^{1}H-NMR [$CDCl_3$ + CD_3OD, 400 MHz] δ 6.94 (t, 1H, N*H*CO), 3.92-3.68 (m, 8H, H-1, H-2', H-3, H-4, H-5, H-6), 3.50-3.37 (m, 3H, H-1'a, H-1'b, H-3'b), 3.19 (dd, 1H, J = 6.7 Hz, H-3'a), 2.19 [t, 2H, $CH_2NC(O)$], 1.60 (m, 2H, CH_2CH_3), 1.30-1.26 (m, 20H, aliphatic H), and 0.88 (t, 3H, J = 6.8 Hz, CH_3) ppm. *Anal* calc for $C_{23}H_{45}NO_8$: C 59.59; H 9.78; N 3.02. Found: C 59.24; H 9.43; N 2.97%.

*2(**R**)-Hydroxy-3-hexadecanoylamidopropyl* β-**D**-*fructopyranoside (**20**)*

Compound **20** (139 mg, 88.5%) was obtained from **17** using the same procedure as described for compound **15**; m.p. 108-109°C: (ether / ethanol). $[\alpha]_D$ –62.3° (DMF); MS (FAB-Na^+) M/z 514.3 (M^++ Na^+), 330 (M^++ Na^+-$C_{13}H_{28}$), 312 (M^++ Na^+-$C_6H_{11}O_6$). ^{13}C-NMR

[$CDCl_3$ + CD_3OD, 75 MHz] δ 174.82 (*C*=O), 99.74 (C-2), 69.89, 69.80, 69.19, 69.13 (C-3, C-4, C-5, C-2'), 63.74 (C-1), 62.90 (C-1'), 62.29 (C-6), 41.50 (C-3'), 36.21 (-CO*C*H_2), 31.68-22.44 (aliphatic C) and 13.77 (*C*H_3) ppm. ^{1}H-NMR [$CDCl_3$ + CD_3OD, 400 MHz] δ 6.95 (t, 1H, N*H*CO), 3.93-3.67 (m, 8H, H-1, H-2', H-3, H-4, H-5, H-6), 3.52-3.36 (m, 3H, H-1'a, H-1'b, H-3'b), 3.19 (dd, 1H, J = 6.7 Hz, H-3'a), 2.20 [t, 2H, C*H*$_2$NC(O)], 1.59 (m, 2H, C*H*$_2$$CH_3$), 1.30-1.26 (m, 24H, aliphatic H), and 0.88 (t, 3H, J = 6.8 Hz, C*H*$_3$) ppm. *Anal* calc for $C_{25}H_{49}NO_8$: C 61.07; H 10.05; N 2.85. Found: C 59.92; H 9.95; N 2.85%.

*2(**R**)-Dodecanoxy-3-dodecanoylamidopropyl 1',3',4',5'-tetra*-O-*benzyl* β-**D**-*fructopyranoside (21)*

A stirred solution of compound **15** (508 mg, 0.639 mmol) in pyridine (10 mL) was treated with lauroyl chloride (0.4 mL, 1.87 mmol, 1.1 eq) in the presence of catalytic amount of 4-dimethylaminopyridine at room temperature for 1 hr. The mixture was then diluted with dichloromethane (50 mL) and washed successively with aqueous hydrochloric acid (2**M**, 20 mL), water (20 mL) and saturated aqueous sodium hydrogen carbonate (20mL). The organic layer was dried ($MgSO_4$), concentrated *in vacuo* and column chromatography (n-hexane-ethyl acetate, 3:1) of the crude material gave **21** (512 mg, 82%) as a pure colourless oil. $[\alpha]_D$ –45.8° ($CHCl_3$). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 173.41, 172.95 (*C*=O), 138.69, 138.41, 137.75, 128.31, 128.20, 127.96, 127.86, 127.69, 127.67, 127.57, 127.52 (aromatic-C), 101.14 (C-2), 79.12 (C-3), 77.41 (C-4), 75.57 (benzylic-C), 73.76 (benzylic-C), 73.54 (C-5), 72.29, 71.35 (benzylic-C), 70.39(C-1), 69.84 (C-2'), 65.80 (C-1'), 61.25 (C-6), 40.64 (C-3'), 36.30 (CO*C*H_2), 31.89 (COCH_2*C*H_2), 29.61-22.65 (aliphatic C), and 14.06, 15.23 (*C*H_3) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.40-7.22 (m, 20H, aromatic H), 6.31 (t, 1H, J = 6.5 Hz, N*H*CO), 4.90 (d, 1H, J = 10.9 Hz, benzylic-H), 4.75, 4.69 (2d, 2H, J = 12.6 Hz, benzylic-H), 4.67-4.60 (m, 4H, benzylic-H), 4.46 (d, 1H, J = 11.8 Hz, benzylic-H), 4.30 (d, 1H, J = 9.9 Hz, H-3), 3.91 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.1 Hz, H-4), 3.88 (dd, 1H, $J_{5,6eq}$ = 1.6 Hz, $J_{6ax,6eq}$ = -12.3 Hz, H-6eq), 3.83 (dd, 1H, $J_{5,6ax}$ = 1.5 Hz, $J_{6ax,6eq}$ =-12.3 Hz, H-6ax), 3.79 (m, 1H, H-5), 3.73-3.28 (m, 7H, H-2', H-1a, H-1b, H-1'a, H-1'b H-3'a, H-3'b), 2.25-1.55 (m, 4H, 2xCOC*H*$_2$$CH_2$), 1.35 (m, 4H, 2xC*H*$_2$$CH_3$), 1.24 (m, 32H, aliphatic H), and 0.87 (2xt, 6H, 2xC*H*$_3$) ppm.

*2(**R**)-Tetradecanoxy-3-tetradecanoylamidopropyl 1',3',4',5'-tetra*-O-*benzyl* β-**D**-*fructopyranoside (22)*

A solution of compound **16** (280 mg, 0.340 mmol) in pyridine (10 mL) was treated with tetradecanoyl chloride (0.1 mL, 0.374 mmol, 1.1 eq) in the same way described above to give compound **22**, which on column chromatography (n-hexane-ethyl acetate, 3:1) gave pure **22** (318.3 mg, 90%) as a colourless oil. $[\alpha]_D$ –54.8° ($CHCl_3$). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 173.39, 172.90 (*C*=O), 138.68, 138.43, 137.76, 128.41, 128.25, 127.95, 127.83, 127.65, 127.69, 127.53, 127.45 (aromatic-C), 101.10 (C-2), 78.55 (C-3), 77.42 (C-4), 75.83, 73.64 (benzylic-C), 73.53 (C-5), 71.93 (benzylic-C), 71.34 (benzylic-C), 70.31 (C-1), 69.82 (C-2'), 67.50 (C-1'), 61.22 (C-6), 40.63 (C-3'), 36.31 (CO*C*H_2), 31.90 (COCH_2*C*H_2), 29.68-22.66 (aliphatic C), and 14.06, 15.23 (*C*H_3) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.39-7.18 (m, 20H, aromatic H), 6.31 (t, 1H, J = 6.5 Hz, N*H*CO), 4.90 (d, 1H, J = 10.9 Hz, benzylic-H), 4.75, 4.69 (2d, 2H, J = 12.6 Hz, benzylic-H), 4.68-4.61 (m, 4H, benzylic-H), 4.45 (d, 1H, J = 11.8 Hz, benzylic-H), 4.30 (d,

1H, J = 9.9 Hz, H-3), 3.90 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.1 Hz, H-4), 3.88 (dd, 1H, $J_{5,6eq}$ = 1.6 Hz, $J_{6ax,6eq}$ = -12.3 Hz, H-6eq), 3.83 (dd, 1H, $J_{5,6ax}$ = 1.5 Hz, $J_{6ax,6eq}$ = -12.3 Hz, H-6ax), 3.79 (m, 1H, H-5), 3.73-3.28 (m, 7H, H-2', H-1a, H-1b, H-1'a, H-1'b, H-3'a, H-3'b), 2.25-1.55 (m, 4H, 2xCOCH_2CH$_2$), 1.35 (m, 4H, 2xCH_2CH$_3$), 1.24 (m, 40H, aliphatic H), and 0.87 (2xt, 6H, 2xCH_3) ppm.

*2(**R**)-Hexadecanoxy-3-hexadecanoylamidopropyl 1',3',4',5'-tetra-*O*-benzyl* β-**D**-*fructopyranoside (23)*

Compound **17** (260 mg, 0.306 mmol) was converted into compound **23** by treatment with hexadecanoyl chloride (0.1 mL, 0.336 mmol, 1.1 eq) using the above procedure. Column chromatography (n-hexane-ethyl acetate, 3:1) of the crude material gave **23** (280.5 mg, 84%) as a colourless oil. $[\alpha]_D$ –46.1° ($CHCl_3$). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 173.10, 172.02 (*C*=O), 138.93, 138.46, 137.78, 128.63, 128.60, 127.96, 127.82, 127.77, 127.69, 127.59, 127.53, 127.45, 127.37 (aromatic-C), 101.10 (C-2), 78.56 (C-3), 77.43 (C-4), 75.85 (benzylic-C), 73.65 (benzylic-C), 73.53 (C-5), 71.94 (benzylic-C), 71.31 (benzylic-C), 70.32 (C-1), 69.46 (C-2'), 67.57 (C-1'), 61.21 (C-6), 40.67 (C-3'), 36.30 (CO*C*H$_2$), 31.90 (COCH$_2$*C*H$_2$), 29.68-22.66 (aliphatic C), 15.23, and 14.06, (*C*H$_3$) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.40-7.20 (m, 20H, aromatic H), 6.31 (t, 1H, J = 6.5 Hz, N*H*CO), 4.92 (d, 1H, J = 10.9 Hz, benzylic-H), 4.77, 4.68 (2d, 2H, J = 12.6 Hz, benzylic-H), 4.68-4.61 (m, 4H, benzylic-H), 4.46 (d, 1H, J = 11.8 Hz, benzylic-H), 4.30 (d, 1H, J = 9.9 Hz, H-3), 3.90 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.1 Hz, H-4), 3.88 (dd, 1H, $J_{5,6eq}$ = 1.6 Hz, $J_{6ax,6eq}$ = -12.3 Hz, H-6eq), 3.83 (dd, 1H, $J_{5,6ax}$ = 1.5 Hz, $J_{6ax,6eq}$ = -12.3 Hz, H-6ax), 3.78 (m, 1H, H-5), 3.73-3.28 (m, 7H, H-2', H-1a, H-1b, H-1'a, H-1'b, H-3'a, H-3'b), 2.25-1.55 (m, 4H, 2xCOCH_2CH$_2$), 1.34 (m, 4H, 2xCH_2CH$_3$), 1.24 (m, 48H, aliphatic H), and 0.87 (2xt, 6H, 2xCH_3) ppm.

*2(**R**)-Dodecanoxy-3-dodecanoylamidopropyl* β-**D**-*fructopyranoside (24)*

A solution of compound **21** (512.3 mg, 0.524 mmol) in methanol (30 mL) was subjected to hydrogenolysis in the presence of palladium on charcoal (10%, 100 mg) at room temperature for 2 hr. The catalyst was removed by filtration, washed with methanol, and the combined filtrate and washings concentrated *in vacuo* to yield compound **24** as white crystals (295 mg, 91%). A sample of the product was crystallized (ether / ethanol) to give pure **24**. m.p. 104°C: $[\alpha]_D$ –55.2° (DMF); MS (FAB-Na^+) M/z 640 (M^++ Na^+), 457 (M^++ Na^+-$COC_{11}H_{23}$), 274 (M^++ Na^+-$COC_{11}H_{23}$ -$COC_{11}H_{23}$), 256 (M^++ Na^+-2x$COC_{11}H_{23}$, -H_2O). ^{13}C-NMR [$CDCl_3$ + CD_3OD, 75 MHz] δ 174.44, 173.39 (*C*=O), 99.85 (C-2), 70.58, 70.47, 70.06, 69.13 (C-3, C-4, C-5, C-2'), 63.46 (C-1), 62.79 (C-1'), 60.04 (C-6), 38.97 (C-3'), 36.40 (-CO*C*H$_2$), 31.76-22.52 (aliphatic C) and 13.92 (*C*H$_3$) ppm. ^{1}H-NMR [$CDCl_3$ + CD_3OD, 400 MHz] δ 6.95 (t, 1H, N*H*CO), 5.03-4.96 (m, 1H, H-2'), 3.92-3.58 (m, 10H, H-1, H-1', H-3, H-3'b, H-4, H-5, H-6), 3.44-3.39 (dd, 1H, J = 6.3Hz, H-3'a), 2.31-2.24 [m, 4H, 2xCH_2C(O)], 1.59 (m, 4H, 2xCH_2CH$_3$), 1.25 (m, 32H, aliphatic H), and 0.88 (2xt, 6H, J = 6.8 Hz, 2xCH_3) ppm. *Anal* calc for $C_{33}H_{63}NO_9$: C 64.15; H 10.28; N 2.27. Found: C 63.76; H 10.47; N 2.28%.

*2(**R**)-Tetradecanoxy-3-tetradecanoylamidopropyl* β-**D**-*fructopyranoside (25)*

Compound **22** (318.3 mg, 0.308 mmol) was treated under the above conditions to give compound **25** (181 mg, 91%) as white crystals. A sample of the product was crystallized (ether / ethanol) to give pure **25**. m.p. 102-103°C: $[\alpha]_D$ –57.3° (DMF); MS (FAB-Na^+) M/z 695 (M^++ Na^+), 512 (M^++ Na^+-$C_{13}H_{27}$), 283 (M^++ Na^+-$C_{13}H_{27}$ -$COC_{13}H_{27}$ -H_2O), ^{13}C-NMR [$CDCl_3$ + CD_3OD, 75 MHz] δ 174.45, 173.41 (*C*=O), 99.69 (C-2), 70.67, 70.44, 70.09, 69.11 (C-3, C-4, C-5, C-2'), 63.48 (C-1), 62.75 (C-1'), 60.06 (C-6), 38.96 (C-3'), 36.41 (-CO*C*H_2), 31.76-22.52 (aliphatic C) and 13.92 (*C*H_3) ppm. ^{1}H-NMR [$CDCl_3$ + CD_3OD, 400 MHz] δ 6.95 (t, 1H, N*H*CO), 5.00-4.96 (m, 1H, H-2'), 3.92-3.58 (m, 10H, H-1, H-1', H-3, H-3'b, H-4, H-5, H-6), 3.45-3.39 (dd, 1H, J = 6.3Hz, H-3'a), 2.32-2.24 (m, 4H, 2xC*H*$_2$C(O)), 1.60 (m, 4H, 2xC*H*$_2$$CH_3$), 1.25 (m, 40H, aliphatic H), and 0.88 (2xt, 6H, J = 6.8 Hz, C*H*$_3$) ppm. *Anal* calc for $C_{37}H_{70}NO_9$: C 66.04; H 10.48; N 2.08. Found: C 65.56; H 10.68; N 2.09%.

*2(**R**)-Hexadecanoxy-3-hexadecanoylamidopropyl* β-**D**-*fructopyranoside (26)*

Conversion of compound **23** (280.5 mg, 0.257 mmol) by hydrogenation using the same procedure as for compound **21** gave compound **26** (107.6 mg, 62%) as white crystals. A sample of the product was crystallized (ether / ethanol) to give pure **26**. m.p. 51.5°C: $[\alpha]_D$ –66.5° (DMF); MS (FAB-Na^+) M/z 752 (M^++ Na^+), 330 (M^++ Na^+-2x$C_{15}H_{31}$), 312 (M^++ Na^+-$C_{15}H_{31}$,-$C_{15}H_{31}$, -H_2O). ^{13}C-NMR [$CDCl_3$ + CD_3OD, 75 MHz] δ 174.47, 173.40 (*C*=O), 99.83 (C-2), 70.59, 70.48, 70.09, 69.14 (C-3, C-4, C-5, C-2'), 63.45 (C-1), 62.76 (C-1'), 60.05 (C-6), 38.98 (C-3'), 36.40 (-CO*C*H_2), 31.76-22.52 (aliphatic C) and 13.92 (*C*H_3) ppm. ^{1}H-NMR [$CDCl_3$ + CD_3OD, 400 MHz] δ 6.94 (t, 1H, N*H*CO), 5.02-4.96 (m, 1H, H-2'), 3.93-3.59 (m, 10H, H-1, H-1', H-3, H-3'b, H-4, H-5, H-6), 3.45-3.39 (dd, 1H, J = 6.3Hz, H-3'a), 2.31-2.24 [m, 4H, 2xC*H*$_2$C(O)], 1.59 (m, 4H, 2xC*H*$_2$$CH_3$), 1.25 (m, 48H, aliphatic H), and 0.88 (2xt, 6H, J = 6.8 Hz, C*H*$_3$) ppm. *Anal* calc for $C_{41}H_{79}NO_9$: C 66.82; H 10.82; N 2.00. Found: C 66.80; H 10.73; N 1.92%.

*2(**R**),3-Bis-(*p*-toluenesulfonyloxy)propyl 1',3',4',5'-tetra*-O-*benzyl* β-**D**-*fructopyranoside (27)*

A stirred, cooled (0°C) solution of **2** (310 mg, 0.5 mmol) in pyridine (5 mL) was treated with *p*-toluenesulfonyl chloride (285 mg, 1.5 mmol, 3 eq) and set aside at room temperature for 48 hr. The mixture was then diluted with dichloromethane (50 mL) and washed successively with aqueous hydrochloric acid (2**M**, 20 mL), water (20 mL) and a solution of saturated aqueous sodium hydrogen carbonate (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (n-hexane-ethyl acetate, 3:1) of the resulting material gave **27** (412.9 mg, 89.5%) as a pure colourless oil. $[\alpha]_D$ –40.4° ($CHCl_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 145.03, 138.91, 138.46, 138.40, 137.74, 132.89, 132.15, 129.80, 129.76, 128.22, 128.14, 128.08, 128.04, 127.88, 127.77, 127.73, 127.62, 127.51, 127.41, 127.24 (aromatic-C), 101.63 (C-2), 78.44 (C-3), 76.49 (C-4), 76.01, 75.18 (benzylic-C), 73.55 (C-5), 73.48 (C-2'), 72.09, 71.19 (benzylic-C), 71.14 (C-1'), 61.37 (C-1), 60.29 (C-6), 59.37 (C-3'), 21.55, 20.95 (*C*H_3) ppm. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.70-7.15 (m, 28H, aromatic H), 4.88, 4.64 (2d, 2H, J = 11.2 Hz, benzylic-H), 4.72, 4.70 (2d, 2H, J = 12.5 Hz, benzylic-H), 4.57, 4.41 (2d, 2H, J = 11.9 Hz, benzylic-H), 4.27 (d, 1H, J = 10.1 Hz, H-3), 4.14 (m, 1H, H-2'), 4.11 (dd, 1H, J = 5.2 Hz, H-1'a), 4.0 (dd, 1H, J = 5.2 Hz, H-1'b), 3.77 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.1 Hz, H-4), 3.72 (m, 1H, H-5), 3.67 (2d, 1H, J = -10.2 Hz,

H-1a), 3.62 (2d, 1H, J = -10.2 Hz, H-1b), 3.60 (dd, 1H, $J_{3'a,2'}$ = 7.3 Hz, H-3'a), 3.54 (dd, 1H, $J_{3'b,2'}$ = 7.3 Hz, H-3'b), and 2.37 (2xs, 6H, 2xCH_3) ppm.

*2(**S**),3-Bis-azidopropyl 1',3',4',5'-tetra-O-benzyl* β-**D**-*fructopyranoside (28)*

A stirred solution of compound **27** (412.9 mg, 0.447 mmol) in DMF (5 mL) containing sodium azide (116.4 mg, 1.79 mmol, 4 eq) was maintained at 80°C for 12 hr. The reaction mixture was concentrated *in vacuo*, treated with a mixture of ether (50 mL) and water (20 mL) and separated organic layer washed with 10% sodium chloride solution (20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Column chromatography of the crude material gave compound **28** (237.5 mg, 80%) as a pure colourless oil. $[\alpha]_D$ – 52.1 ($CHCl_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 138.75, 138.49, 138.43, 137.74 128.28, 128.13, 128.00, 127.85, 127.70, 127.60, 127.48, 127.37 (aromatic-C), 101.66 (C-2), 78.49 (C-3), 76.21 (C-4), 75.37 (benzylic-C), 73.65 (C-5), 73.61, 72.26, 71.33 (benzylic-C), 70.40 (C-1'), 62.17 (C-6), 61.53 (C-1), 61.15 (C-2'), and 51.63 (C-3') ppm. ^{1}H-NMR ($CDCl_3$, 400M Hz) δ 7.40-7.23 (m, 20H, aromatic H), 4.92, 4.66 (2d, 2H, J = 11.3 Hz, benzylic-H), 4.75, 4.74 (2d, 2H, J = 12.6 Hz, benzylic-H), 4.59, 4.37 (2d, 2H, J = 11.9 Hz, benzylic-H), 4.30 (d, 1H, J = 10.1 Hz, H-3), 4.03 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.1 Hz, H-4), 3.80 (m, 1H, H-5), 4.0(dd, 1H, J = 5.2 Hz, H-1'b), 3.70 (2d, 1H, J = -10.2 Hz, H-1a), 3.67 (m, 1H, H-2'), 3.62 (2d, 1H, J = -10.2 Hz, H-1b), 3.33 (dd, 1H, $J_{3'a,2'}$ = 4.6, H-3'a), 3.2 (dd, 1H, $J_{3'b,2'}$ = 7.3 Hz, H-3'b) ppm.

*2(**S**),3-Diaminopropyl 1',3',4',5'-tetra*-O-*benzyl* β-**D**-*fructopyranoside (29)*

A stirred, cooled (0°C) solution of **28** (237.5 mg, 0.357 mmol) in dry ether (5 mL) was treated portionwise with lithium aluminium anhydride (47.5 mg, 1.25 mmol, 3.5 eq) and then kept aside at room temperature for 30 mins. The reaction was quenched by addition of ether (10 mL) and water (0.5 mL), filtered through $MgSO_4$, the inorganic material washed with ether (10 mL) and the combined filtrate and washings concentrated *in vacuo*. Column chromatography (methanol-dichloromethane, 1:4) of the crude material gave **29** (190.1 mg, 83.4%) as a pure colourless oil. $[\alpha]_D$ –45.2° ($CHCl_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 138.88, 138.51, 138.40, 137.90, 128.25, 128.13, 127.82, 127.79, 127.74, 127.65, 127.62, 127.51, 127.47, 127.31 (aromatic-C), 101.31 (C-2), 78.52 (C-3), 76.36 (C-4), 75.38 (benzylic-C), 73.56 (C-5), 73.44, 71.99, 71.19 (benzylic-C), 70.23 (C-1'), 64.55 (C-6), 61.13 (C-1), 52.96 (C-2'), and 45.30 (C-3') ppm. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.40-7.21 (m, 20H, aromatic H), 4.91, 4.66 (2d, 2H, J = 11.2 Hz, benzylic-H), 4.76, 4.70 (2d, 2H, J = 12.5 Hz, benzylic-H), 4.60, 4.43 (2d, 2H, J = 11.9 Hz, benzylic-H), 4.35 (d, 1H, J = 10.0 Hz, H-3), 3.92 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.0 Hz, 4), 3.85 (m, 1H, H-5), 3.64 (2d, 1H, J = -10.2 Hz, H-1a), 3.59 (2d, 1H, J = -10.2 Hz, H-1b), 2.9 (m, 1H, H-2'), 2.72 (dd, 1H, $J_{3'a,2'}$ = 4.3 Hz, H-3'a), 2.58 (dd, 1H, $J_{3'b,2'}$ = 7.3 Hz, H-3'b), and 2.0 (s, 4H, NH_2) ppm.

*2(**S**),3-Bis-dodecanoylamidopropyl 1',3',4',5'-tetra*-O-*benzyl* β-**D**-*fructopyranoside (30)*

A stirred cooled (0°C) solution of compound **29** (190 mg, 0.297 mmmol) in a mixture of dichloromethane (10 mL) and triethylamine (0.6 mL) was treated with lauroyl chloride (0.19 mL, 0.891 mmol, 3 eq) and set aside for 1 hr. The mixture was diluted with more

dichloromethane (50 mL) and washed successively with aqueous hydrochloric acid (2M, 20 mL), water (20 mL) and saturated aqueous sodium hydrogen carbonate (20 mL) dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (n-hexane-ethyl acetate, 3:1) of the crude material gave compound **30** (252.3 mg, 87.0%) as a pure colourless oil. $[\alpha]_D$ –31.0° ($CHCl_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 174.75, 173.96 (*C*=O), 138.68, 138.27, 138.23, 137.64, 128.41, 128.34, 128.31, 128.27, 128.21, 128.18, 128.13, 127.99, 127.83, 127.81, 127.75, 127.71, 127.69, 127.66, 127.64, 127.58(aromatic-C), 100.87 (C-2), 78.81 (C-3), 77.19 (C-4), 75.74, 73.82 (benzylic-C), 73.06 (C-5), 71.98, 71.73 (benzylic-C), 71.21 (C-1), 61.12 (C-1'), 60.82 (C-6), 49.37 (C-2'), 42.17 (C-3'), 36.43, 36.29 ($COCH_2$), 31.83-22.63 (aliphatic C), 14.07, and 14.05 (CH_3) ppm. ^{1}H-NMR ($CDCl_3$, 400M Hz) δ 7.39-7.22 (m, 20H, aromatic H), 6.94 (d, 1H, J = 7.3 Hz N*H*CO), 6.45 (t, 1H, J = 6.5 Hz N*H*CO), 4.95, 4.61 (2d, 2H, J = 10.7 Hz, benzylic-H), 4.75, 4.68 (2d, 2H, J = 12.5 Hz, benzylic-H), 4.63, 4.46 (2d, 2H, J = 11.8 Hz, benzylic-H), 4.30 (d, 1H, J = 9.9 Hz, H-3), 3.91 (m, 1H, H-2'), 3.90 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.1 Hz, H-4), 3.87 (dd, 1H, $J_{5,6eq}$ = 1.6 Hz, $J_{6ax,6eq}$ = -12.3 Hz, H-6eq), 3.84 (dd, 1H, $J_{5,6ax}$ = 1.5 Hz, $J_{6ax,6eq}$ = -12.3 Hz, H-6ax), 3.74 (m, 1H, H-5), 3.70 (2d, 1H, J = -10.2 Hz, H-1a), 3.62 (2d, 1H, J = -10.2 Hz, H-1b), 3.31 (dd, 1H, $J_{3'a,2'}$ = 6.4 Hz, 3'a), 3.30 (dd, 1H, $J_{3'b,2'}$ = 6.4 Hz, H-3'b), 1.99 (t, 2H, $COCH_2$), 1.91 (t, 2H, $COCH_2$), 1.29 (m, 32H, aliphatic H), and 0.87 (2xt, 6H, $2xCH_3$) ppm.

*2(**S**),3-Bis-tetradecanoylamidopropyl 1',3',4',5'-tetra-*O*-benzyl β-**D**-fructopyranoside (31)*

Treatment of compound **29** (229 mg, 0.359 mmol) with tetradecanoyl chloride (0.22 mL, 1.077 mmol, 3 eq) in the above manner gave compound **31**. Column chromatography (n-hexane-ethyl acetate, 3:1) of the crude material gave **31** (293 mg, 81.3%) as a pure colourless oil $[\alpha]_D$ – 28.7° ($CHCl_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 174.79, 173.97 (*C*=O), 138.77, 138.31, 138.27, 137.67, 128.35, 128.30, 128.24,127.98, 127.87, 127.78, 127.69, 127.59, 127.55 (aromatic-C), 100.89 (C-2), 78.61 (C-3), 76.57 (C-4), 75.52, 73.77 (benzylic-C), 73.00 (C-5), 71.74, 71.76 (benzylic-C), 71.23 (C-1), 70.36 (C-2'), 61.14 (C-1'), 60.87 (C-6), 49.40 (C-2'), 42.25 (C-3'), 36.46, 36.31 ($COCH_2$), 31.89-22.66 (aliphatic C), 14.09, and 14.05 (CH_3) ppm. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.56-7.21 (m, 20H, aromatic H), 6.89 (d, 1H, J = 7.3 Hz N*H*CO), 6.40 (t, 1H, J = 6.5 Hz N*H*CO), 4.95, 4.63 (2d, 2H, J = 10.7 Hz, benzylic-H), 4.75, 4.68 (2d, 2H, J = 12.5 Hz, benzylic-H), 4.57, 4.47 (2d, 2H, J = 11.8 Hz, benzylic-H), 4.30 (d, 1H, J = 9.9 Hz, H-3), 4.04 (m, 1H, H-2'), 3.92 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.2 Hz, H-4), 3.87 (m, 1H, H-5), 3.72 (2d, 1H, J = -10.2 Hz, H-1a), 3.62 (2d, 1H, J = -10.2 Hz, H-1b), 3.30 (dd, 1H, $J_{3'a,2'}$ = 6.4 Hz, H-3'a), 3.26 (dd, 1H, $J_{3'b,2'}$ = 6.4 Hz, H-3'b), 2.01 (t, 2H, $COCH_2$), 1.91 (t, 2H, $COCH_2$), 1.55-1.48 (2xt, 4H, CH_2CH_3), 1.25 (m, 40H, aliphatic H), and 0.87 (2xt, 6H, $2xCH_3$) ppm.

*2(**S**),3-Bis-hexadecanoylamidopropyl 1',3',4',5'-tetra-*O*-benzyl β-**D**-fructopyranoside (32)*

Compound **29** (253 mg, 0.396 mmol) was treated with hexadecanoyl chloride (0.25 mL, 1.188 mmol, 3 eq) in the same manner. Column chromatography (n-hexane-ethyl acetate, 3:1) of the material product gave **32** (387.14 mg, 94.6%) as a pure colourless oil $[\alpha]_D$ –25.7 ($CHCl_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 174.75, 173.94 (*C*=O), 138.76, 138.29, 138.26, 137.66, 128.34, 128.32, 128.27, 128.21, 128.12, 127.95, 127.92, 127.87, 127.84, 127.82, 127.80, 127.78, 127.75, 127.73, 127.71, 127.67 (aromatic-C), 100.88 (C-2), 78.59 (C-3), 76.92 (C-4), 75.49, 73.75

(benzylic-C), 73.01 (C-5), 71.74, 71.21 (benzylic-C), 70.35 (C-1), 70.33 (C-2'), 61.12 (C-1'), 60.82 (C-6), 49.37 (C-2'), 42.17 (C-3'), 36.44, 36.29 ($COCH_2$), 31.87-22.64 (aliphatic C), 14.07, and 14.05 (CH_3) ppm. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.39-7.22 (m, 20H, aromatic H), 6.89 (d, 1H, J = 7.3 Hz N*H*CO), 6.42 (t, 1H, J = 6.5 Hz N*H*CO), 4.95, 4.63 (2d, 2H, J = 10.7 Hz, benzylic-H), 4.75, 4.68 (2d, 2H, J = 12.5 Hz, benzylic-H), 4.63, 4.46 (2d, 2H, J = 11.8 Hz, benzylic-H), 4.30 (d, 1H, J = 9.9 Hz, H-3), 4.06 (m, 1H, H-2'), 3.92 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.1 Hz, H-4), 3.87 (m, 1H, H-5), 3.70 (2d, 1H, J = -10.2 Hz, H-1a), 3.62 (2d, 1H, J = -10.2 Hz, H-1b), 3.31 (dd, 1H, $J_{3'a,2'}$ = 6.4 Hz, H-3'a), 3.30 (dd, 1H, $J_{3'b,2'}$ = 6.4 Hz, H-3'b), 2.0 (t, 2H, $COCH_2$), 1.99 (t, 2H, $COCH_2$), 1.52-1.48 (2xt, 4H, CH_2CH_3), 1.29 (m, 48H, aliphatic H), and 0.87 (2xt, 6H, 2xCH_3) ppm.

*2(**S**),3-Bis-dodecanoylamidopropyl* β-**D**-*fructopyranoside (33)*

A solution of compound **30** (186.5 mg, 0.191 mmol) in methanol (30 mL) was subjected to hydrogenolysis in the presence of palladium on charcoal (10%, 60 mg) at room temperature for 2 hr in the usual manner. The catalyst was removed by filtration, washed with methanol and the combined filtrate and washings concentrated *in vacuo* to yield compound **33** as white crystals (83.8 mg, 71.2%). A sample of the product was crystallized (ether / ethanol) to give pure **33**. m.p 110-112°C; $[\alpha]_D$ –48.5° (DMF); MS (FAB-Na^+) M/z 639 (M^++ Na^+), 456 (M^++ Na^+-$COC_{11}H_{23}$), 273 (M^++ Na^+ –$COC_{11}H_{23}$ –$COC_{11}H_{23}$), 256 (M^++ Na^+ –$COC_{11}H_{23}$ – $COC_{11}H_{23}$ –OH). ^{13}C-NMR [$CDCl_3$ + CD_3OD, 75 MHz] δ 175.41, 174.88 (*C*=O), 99.62(C-2), 70.51 (C-3), 69.74 (C-4), 69.14 (C-5), 63.84 (C-1), 62.69 (C-6), 60.42 (C-1'), 49.36 (C-2'), 40.56 (C-3'), 36.42, 36.37 (-$COCH_2$), 31.73-22.49 (aliphatic C) and 13.86 (CH_3) ppm. ^{1}H-NMR [$CDCl_3$ + CD_3OD, 400 MHz] δ 4.0 (m, 1H, H-2'), 3.91 (d, 1H, J = 9.9 Hz, H-3), 3.84 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.2 Hz, H-4), 3.68 (m, 1H, H-5), 3.58 (dd, 1H, $J_{3'a,2'}$ = 3.6 Hz, H-1'a), 3.45 (dd, 1H, $J_{3'b,2'}$ = 3.6, H-1'b), 3.47 (dd, 1H, J = 4.8 Hz, H-3'a), 3.36 (dd, 1H, J = 4.8 Hz, H-3'b), 2.1 (tx2, 4H, $COCH_2$), 1.58 (m, 4H, $CH_2CH_2CH_3$), 1.25 (m, 32H, aliphatic H), and 0.87 (2xt, 6H, 2xCH_3) ppm. *Anal* calc for $C_{33}H_{64}N_2O_8$: C 64.25; H 10.46; N 4.54. Found: C 63.91; H 10.49; N 4.55%.

*2(**S**),3-Bis-tetradecanoylamidopropyl* β-**D**-*fructopyranoside (34)*

Hydrogenolysis of compound **31** (303.7 mg, 0.287 mmol) in methanol (30 mL) in the same procedure as above gave compound **34** (123.7 mg, 66.9%) as white crystals (ether / ethanol). m.p. 145°C; $[\alpha]_D$ –48.5° (DMF); MS (FAB-Na^+) M/z 667(M^++ Na^+), 484 (M^++ Na^+-$C_{13}H_{27}$), 301 (M^++ Na^+-$C_{13}H_{27}$ –$COC_{13}H_{27}$), 284 (M^++ Na^+-$C_{13}H_{27}$ –$COC_{13}H_{27}$ –OH). ^{13}C-NMR [$CDCl_3$ + CD_3OD, 75 MHz] δ 175.17, 174.72 (*C*=O), 99.60(C-2), 69.76 (C-3), 69.56 (C-4), 68.99 (C-5), 63.68 (C-1), 62.22 (C-6), 60.27 (C-1'), 48.64 (C-2'), 40.26 (C-3'), 36.02 ($COCH_2$), 35.95 ($COCH_2$), 31.48-22.21 (aliphatic C) and 13.45 (CH_3) ppm. ^{1}H-NMR [$CDCl_3$ + CD_3OD, 400 MHz] δ 3.87 (m, 1H, H-2'), 3.69 (d, 1H, J = 9.9 Hz, H-3), 3.66 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.4 Hz, H-4), 3.49 (m, 1H, H-5), 3.40 (dd, 1H, $J_{3'a,2'}$ = 3.6 Hz, H-1'a), 3.37 (dd, 1H, $J_{3'b,2'}$ = 3.6, H-1'b), 3.23 (dd, 1H, J = 4.8Hz, H-3'a), 3.17 (dd, 1H, J = 4.8 Hz, H-3'b), 1.95 (2xt, 4H, $COCH_2$), 1.36 (m, 4H, $CH_2CH_2CH_3$), 1.06 (m, 40H, aliphatic H), and 0.65 (2xt, 6H, 2xCH_3) ppm. *Anal* calc for $C_{35}H_{68}N_2O_8$: C 65.18; H 10.63; N 4.34. Found: C 65.73; H 10.89; N 4.17%.

2(S),3-Bis-hexadecanoylamidopropyl β-D-fructopyranoside (35)

Hydrogenolysis of compound **32** (612 mg, 0.593 mmol) in methanol (30 mL) in the above described manner gave compound **35** (260 mg, 65.2%) as white crystals (ether / ethanol). m.p 150°C; $[\alpha]_D$ –47.4° (DMF); MS (FAB-Na^+) M/z 695 (M^++ Na^+), 273 (M^++ Na^+-2x$C_{15}H_{31}$), 256 (M^++ Na^+-$C_{15}H_{31}$ -$C_{15}H_{31}$ -OH). ^{13}C-NMR [$CDCl_3$ + CD_3OD, 75 MHz] δ 175.64, 174.80 (*C*=O), 99.60 (C-2), 70.51 (C-3), 69.73 (C-4), 69.14 (C-5), 63.82 (C-1), 62.68 (C-6), 60.42 (C-1'), 49.36 (C-2'), 40.56 (C-3'), 36.42, 36.37 (-CO*C*H_2), 31.73-22.49 (aliphatic C) and 13.86 (*C*H_3) ppm. ^{1}H-NMR [$CDCl_3$ + CD_3OD, 400 MHz] δ 3.90 (m, 1H, H-2'), 3.70 (d, 1H, J = 9.9 Hz, H-3), 3.62 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.4 Hz, H-4), 3.46 (m, 1H, H-5), 3.39 (dd, 1H, $J_{3'a,2'}$ = 3.6 Hz, H-1'a), 3.36 (dd, 1H, $J_{3'b,2'}$ = 3.6 Hz, H-1'b), 3.23 (dd, 1H, J = 4.8 Hz, H-3'a), 3.17 (dd, 1H, J = 4.8 Hz, H-3'b), 1.95 (2xt, 4H, CO*C*H_2), 1.34 (m, 4H, $CH_2C\mathit{H}_2CH_3$), 1.10 (m, 48H, aliphatic H), and 0.66 (2xt, 6H, 2x*C*H_3) ppm. *Anal* calc for $C_{37}H_{72}N_2O_8$: C 66.03; H 10.78; N 4.16. Found: C 65.96; H 10.74; N 3.89%.

5.5 References

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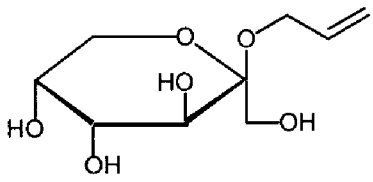
CHAPTER 6

SYNTHESIS AND SOME REACTIONS OF BUT-2-ENYL β-D-FRUCTOPYRANOSIDE

6.1 Introduction

The simple synthesis of allyl β-D-fructopyranoside (**1**) by reaction of D-fructose (**2**) with allyl alcohol containing *ca* 1% hydrogen chloride has been reported [1] (see Chapter 3). Attempts to obtain **1** from sucrose or inulin, using the same procedure, were unsuccessful.[1] Treatment of D-fructose (**2**) with propargyl alcohol also failed to give the corresponding propargyl β-D-fructopyranoside (**3**). These results indicated that the application of the glycosidation procedure to fructose is fairly limited and very sensitive to small changes in the reactants (alcohols). It was considered of interest to perform further investigations on the direct glycosidation of D-fructose (**2**) using the same conditions employed in the synthesis of allyl β-D-fructopyranoside.[2] Direct glycosidation of D-fructose (**2**) with but-2-en-1-ol (crotyl alcohol) yielded but-2-enyl β-D-fructopyranoside (**4**) as a potentially useful intermediate for the synthesis of analogues related to 1-*O*-β-D-fructopyranosyl-*sn*-glycerol [2,3-dihydroxypropyl β-D-fructopyranoside.(**5**)].

Alkenyl glycosides and their derivatives have been used for the synthesis of various other glycosides, e.g. epoxyalkyl glycosides [3-5] as putative inhibitors of β-D-glucan hydrolases.[4,6] The syntheses of these compounds are normally carried out using modified Koenigs-Knorr procedures. This approach was not considered applicable to D-fructose. Koenigs-Knorr-type procedures are fraught with difficulties when applied to **2** because of a lack of suitably protected, activated intermediates and complications arising from competitive orthoester formation.



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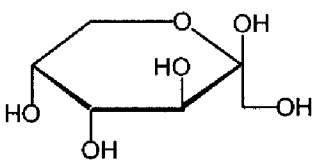

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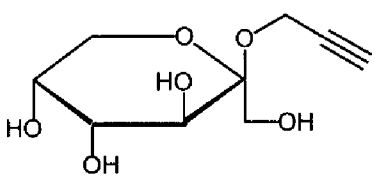

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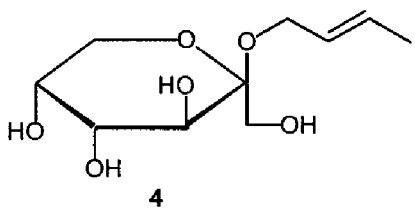

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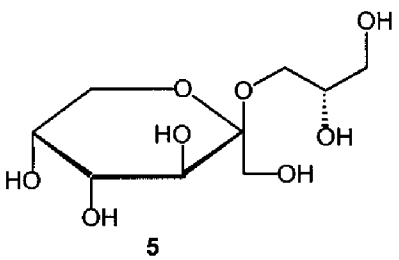

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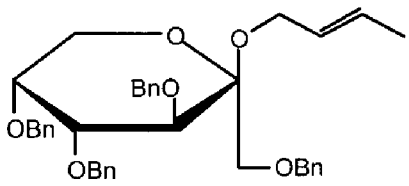
The contents of this chapter discuss the synthesis of but-2-enyl β-D-fructopyranoside (**4**) and some of its oxidation reactions, these were directed at obtaining compounds related to the derivatives obtained from **5** (see previous chapters). These include conversion to a diol by

asymmetric dihydroxylation reactions (Sharpless type), proof of configuration of the introduced chiral centres, and formation of some long-chain acylated amino derivatives obtained *via* azido intermediates, some acylated aziridines, and a study of their ring opening reactions with dibenzyl hydrogen phosphate. The subsequent formation of the unprotected amino acyl monophosphoric acid derivatives as phospholipid models will also be described.

6.2 Results and discussion

6.2.1 Synthesis of but-2-enyl β-D-fructopyranoside (4)

The synthesis of compound **4** involved the acid catalyzed reaction of D-fructose (**2**) with 2-buten-1-ol in a manner similar to that described [1,2] for **1**. Compound **2** was treated with but-2-en-1-ol (crotyl alcohol, *cis-trans*, 1:19) in the presence of a catalytic quantity of acetyl chloride at room temperature for *ca* 48 hr. The reaction mixture remained heterogeneous throughout this period and crystalline **4** was obtained in 55-65% yield after purification. The addition of more D-fructose (**2**) to the filtrate of this reaction resulted in a further yield of **4** (10%). Catalytic reduction of **4** under condition described previously,[2] gave the known butyl β-D-fructopyranoside (**7**). The low yield of the second crop in this case is in contrast to the yield obtained when the filtrates obtained from the reaction of **1** with allyl alcohol are treated [1,2] under the same conditions. Treatment of **4** in dimethyl sulfoxide solution with benzyl chloride, in the presence of powdered potassium hydroxide, gave the perbenzylated glycoside **6** (88%), after purification by column chromatography. This protected derivative was used as the basis substrate in all of the following experiments.



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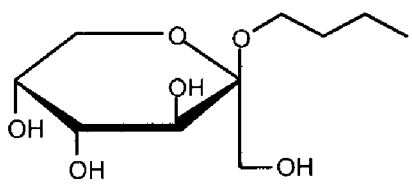

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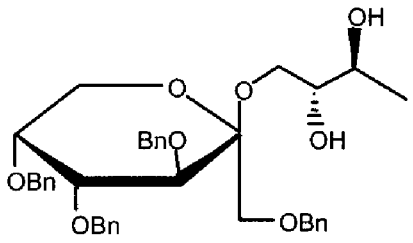
6.2.2 Asymmetric dihydroxylation of but-2-enyl 1,3,4,5-tetra-*O*-benzyl β-D-fructo-pyranoside (6)

Catalytic asymmetric dihydroxylations (Sharpless type) have been used for the oxidation of various alkenyl glycosides.[7] The application of chiral ligands in these procedures, mainly the cinchona type alkaloids have improved the stereoselectivity of some asymmetric dihydroxylation reactions.[8,9] In this case the asymmetric dihydroxylation reactions were performed using phthalazine ligands, 1,4-bis(9-*O*-dihydroquinidine)phthalazine $(DHQD)_2$-PHAL and 1,4-bis(9-*O*-dihydroquinine)phthalazine $(DHQ)_2$-PHAL. Catalytic asymmetric dihydroxylation (Sharpless type) reactions of compound **6** were carried out at room temperature. The reactions were accelerated by the addition of methanesulfonamide.[10-12] The addition of

methanesulfonamide to these reactions enhances the rate of hydrolysis of the intermediate osmate esters that are formed.[10] Osmium-catalyzed asymmetric dihydroxylation reactions of **6** in water / t-butyl alcohol (1:1) mixture in the presence of $(DHQD)_2$-PHAL and $(DHQ)_2$-PHAL as chiral ligands gave the diol **8** in 73% and 76.5% yields, respectively, after *ca* 4 hr.[13] Catalytic hydrogenolysis (palladium-carbon) and subsequent acetylation of **8**, performed under the usual condition, yielded the acetylated products **9**. The GLC analysis carried out on these acetylated products indicated high stereoselectivity for both dihydroxylation reactions (AD mix β, d.e. = 97.3% and AD mix α, d.e. = 96.2%), but, surprisingly, also suggested that both products were identical.



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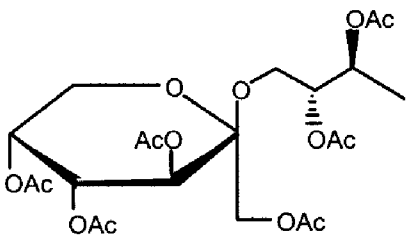

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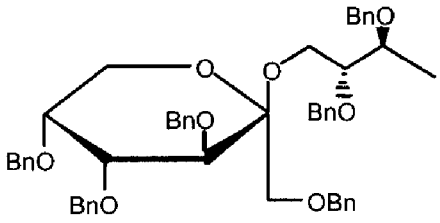
The absolute configuration of the chiral carbons in the aglycon moiety of compound **8** derived from dihydroxylation reactions in the presence of $(DHQD)_2$-PHAL and $(DHQ)_2$-PHAL was then confirmed using hydrolysis / derivatization procedures. Compound **10**, derived from the diol **8** by benzylation under basic condition, was subjected to acidic cleavage performed with trifluoroacetic acid / water (9:1) mixture. The resultant triol derivative **11** of the cleavage reaction was then converted to 1,2,3-butanetriol (**12**) by catalytic hydrogenation (H_2, Pd/C) in methanol. Reaction of **12** with *p*-nitrobenzoyl chloride in pyridine gave the tris(4-nitrobenzoyl) derivative **13**. The physical properties (melting point and optical rotation) of the compound obtained **13** corresponded well with the data reported for the tris(4-nitrobenzoyl) derivative of (2'*R*),(3'*R*) 1,2,3-butanetriol (**12**) [14-16](see experimental section). From these results, compound **8** was characterized as 2(*R*),3(*R*)-dihydroxybutyl 1,3,4,5-tetra-*O*-benzyl-β-D-fructopyranoside. It was expected that the diol derived using $(DHQ)_2$-PHAL as a chiral ligand would differ stereo-chemically (C-2 and C-3) from that obtained by asymmetric dihydroxylation in the presence of $(DHQD)_2$-PHAL. It is of interest to note that the physical properties (melting point and optical rotation) of the tris(4-nitrobenzoyl) derivative of 1,2,3-butanetriol derived from the diol obtained using $(DHQ)_2$-PHAL were of the same magnitude to those obtained in the previous case. Once again (see chapter 3) the expected alteration of stereochemistry using this ligand was not observed. Seemingly, intramolecular stereocontrol by the fructose unit prevails over the molecular control by the chiral dihydroxylation catalyst.



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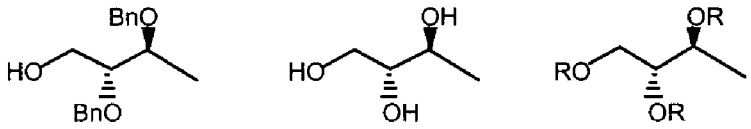


11 **12** **13**

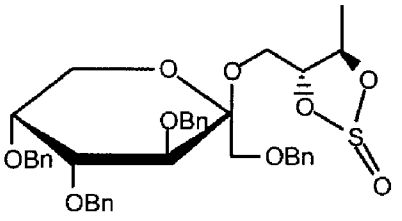
R= p-NO_2benzoyl

6.2.3 Synthesis and reactions of *2(R)*-hydroxy,*3(S)*-aminobutyl 1',3',4',5'-tetra-*O*-benzyl-β-D-fructopyranoside (19) and (*2S*),(*3S*)-aziridinobutyl 1',3',4',5'-tetra-*O*-benzyl-β-D-fructopyranoside (21)

A synthetic sequence for the conversion of **8** into (2*R*) hydroxy-(3*S*)-azidobutyl 1',3',4',5'-tetra-*O*-benzyl β-D-fructopyranoside (**17a**) and thence to amino alcohol **19** and aziridine **21** was then carried out. Compounds **19** and **21** were required as intermediates in the syntheses of some mono-acylamino and *N*-acylated aziridine derivatives which could possess amphiphilic properties and act as potential amide-containing surfactants (see also chapter 5 and 7).

Treatment of **8** with thionyl chloride in presence of a base (triethylamine) gave the cyclic sulfite **14** which was converted to the more stable sulfate **15** in 76-85% overall yield by periodate oxidation catalyzed by ruthenium oxide. Transformation of the cyclic sulfate **15** to the corresponding azido alcohol **17** involved reaction of **15** in *N,N*-dimethylformamide solution with lithium azide.[17-20] Nucleophilic ring-opening of cyclic sulfates, in most cases, gives a mixture of two isomers. Cyclic sulfate **15** could be converted either into the azido sulfates **16a** or **16b**, or to both depending on the reaction conditions. The azide ion attacks preferentially at the terminal carbon of the cyclic sulfate, which is the least hindered, and sometimes high selectivity is observed during the reaction. Interestingly, this reaction led to the preponderant formation of the regioisomer **16a** resulting from nucleophilic attack of azide ion at C-3 of cyclic sulfate **15**. These results were supported by ^{1}H and ^{13}C-NMR spectra of compound **17a** obtained by brief treatment of **16a** in THF with concentrated sulfuric acid. The nucleophilic attack by azide ion at C-3 could easily be deduced from the ^{1}H-NMR spectrum by the presence of triple doublets (ddd) at δ = 3.5 ppm, arising from H-2 coupled with H-1 and H-3. The chemical shift of H-2 at the low field is due to the presence of the hydroxyl group at C-2. More evidence for the position of the hydroxyl group at C-2, as well as the position of the azido group on C-3 were obtained from ^{13}C-NMR, and 2D-COSY spectra. The ^{13}C-NMR of **17a** showed the presence of a signal

expected for an azido group on the terminal position (C-3 = 58.68 ppm). The position of the hydroxyl group could also be deduced from DEPT-135 experiments, which indicated a signal for carbon bearing a hydroxyl group (C-2) at 73.45 ppm. The results from ^{1}H and ^{13}C-NMR analyses were confirmed by 2D-COSY spectra. The (H,H)-COSY experiment showed the coupling of H-2 with H-1 and H-3. Results from the (C,H)-COSY experiment confirmed the correlation between C-2 and H-2 and, C-3 and H-3. The combined results, and observations from analyses of other spectroscopic data strongly supported the formation of regioisomer **17a** resulting from nucleophilic attack by azide ions at C-3 of **15**.



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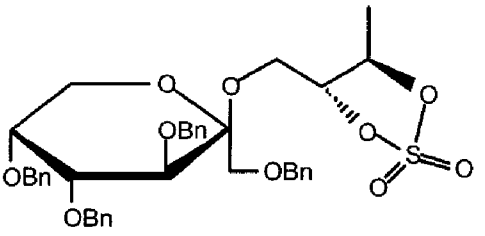

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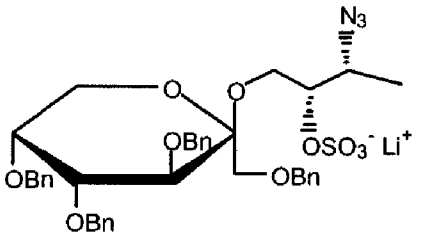
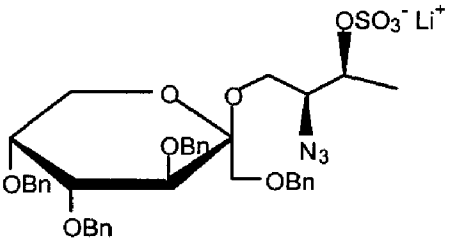
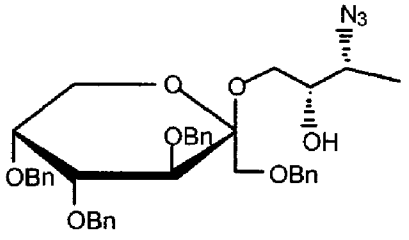


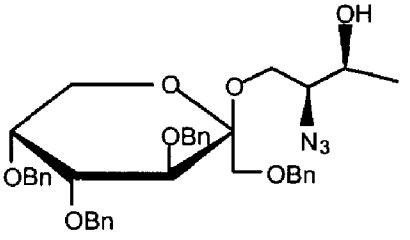
16a



16b



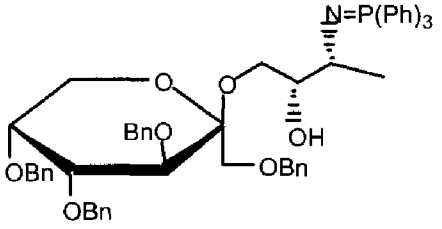
17a



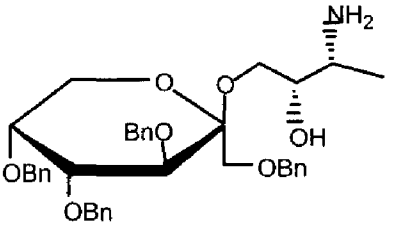
17b

The second step of the sequence involved the conversion of the azido alcohol **17a** into the corresponding amino alcohol **19** and the aziridine **21**. The azido alcohol **17a** can either be converted directly to the amino alcohol by reduction of the azido group, or can be made to undergo subsequent cyclization to form the corresponding aziridine **21** by reduction of the azido group in the presence of a good leaving group, e.g. a sulfonate ester. The reduction of the azido group to an amino group utilizing triphenylphosphine [21] was chosen for this purpose. This synthetic procedure requires mild condition and is one of the most selective routes used for the transformation of an azido to an amino group. The reaction of **17a** with triphenylphosphine gave the corresponding amino alcohol **19**. The intermediate **18** was formed during the reaction probably by extrusion of nitrogen from the azide function of **17a**. This intermediate was not isolated but hydrolyzed to the amino alcohol **19** (74.5%).[22,23]

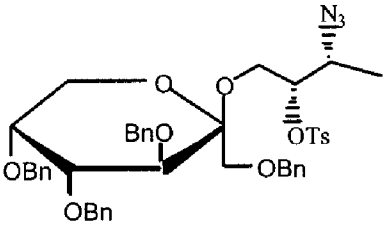
The conversion of the azido alcohol **17a** into the corresponding aziridine **21** was accomplished using a standard procedure, involving treatment of **17a** with *p*-toluenesulfonyl chloride / pyridine, followed by reaction of the resultant monosulfonated intermediate **20** (80%) with lithium aluminium hydride in tetrahydrofuran to give the aziridine **21** (68.8%).



18



19



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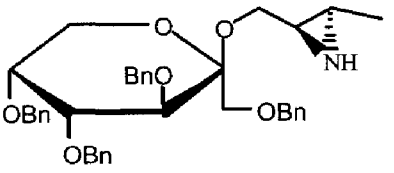
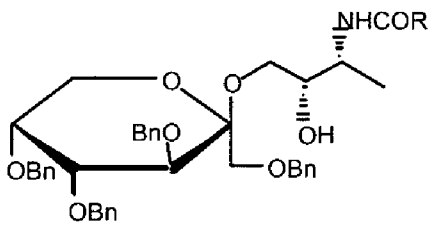
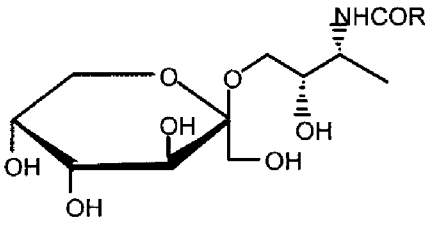


21

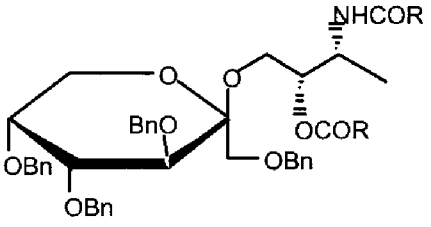
The synthesis of amide derivatives of the amino alcohol **19** was then investigated using two synthetic routes. Both of these routes involved acylation reactions using fatty acid chlorides (lauroyl, myristoyl or palmitoyl) as the acylating agents. For the preparation of amide derivatives **22**, **23**, and **24**, low temperatures were required to control the selectivity of the two reaction centres (hydroxyl *vs* amino function) of **19** in the acylation reactions. The reaction of the amino alcohol **19** in dichloromethane solution at 0°C under basic conditions with an equivalent of fatty acid chloride (lauroyl, myristoyl or palmitoyl) yielded the corresponding amide derivatives **22**, **23**, and **24** in good yields (70-79%). The second procedure for the synthesis of amide derivatives **25**, **26**, and **27** involved reactions performed at room temperature. The conversion of **22**, **23**, and **24** to the corresponding amide derivatives **25**, **26**, and **27** was performed in pyridine solution with an excess fatty acid chloride, in the presence of catalytic amount of 4-*N*,*N*-dimethylaminopyridine. The yields of the resultant products **25**, **26**, and **27** were in the range of 70-80%. The unprotected amide derivatives **28-33** (70-90%) were obtained by catalytic hydrogenolysis (H_2, Pd/C) of the compounds **22-27** in methanol in the usual manner.



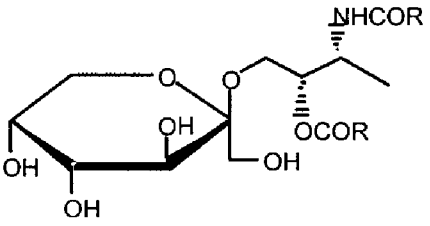
22 R =$C_{11}H_{23}$ (70%)
23 R =$C_{13}H_{27}$ (79.3%)
24 R =$C_{15}H_{31}$ (72.2 %)



28 R =$C_{11}H_{23}$ (83.2%)
29 R =$C_{13}H_{27}$ (78%)
30 R =$C_{15}H_{31}$ (93%)



25 R =$C_{11}H_{23}$ (76.4 %)
26 R =$C_{13}H_{27}$ (72.5%)
27 R =$C_{15}H_{31}$ (80.9 %)

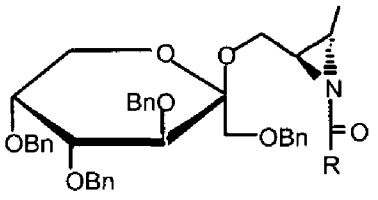


31 R =$C_{11}H_{23}$ (84.9%)
32 R =$C_{13}H_{27}$ (81%)
33 R =$C_{15}H_{31}$ (73.5%)

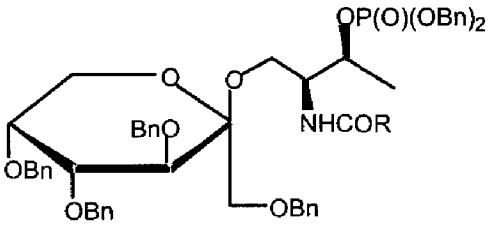
Activation of the aziridine ring of compound **21** for nucleophilic ring-opening reactions through *N*-acylation was also considered. The *N*-acyl aziridine derivatives of **21** were readily prepared using fatty acid chlorides under standard conditions. Treatment of a solution of **21** in dichloromethane at -18°C with various fatty acid chlorides in the presence of triethylamine as a base gave the corresponding *N*-acyl aziridine derivatives **34**, **35**, and **36**. Nucleophilic ring-opening of these activated derivatives using dibenzyl hydrogen phosphate was then performed at room temperature. The choice of dibenzyl hydrogen phosphate as a nucleophile for the nucleophilic reactions was based on previous results from the synthesis of optically active amide-containing surfactants.[24] (see Chapter 7 for further details). Nucleophilic attack on the *N*-acyl aziridine ring of **34**, **35**, and **36** can take place at either carbon atom of the *N*-acylated aziridine rings. This depends on the reaction conditions and the reactivity of both carbon atoms involved in reaction. Nucleophilic ring-opening reactions of the derivatives **34**, **35**, and **36** led to the preponderant formation of only one regio-isomer in each case to give compounds **37**, **38**, and **39**. These observations were supported by ^{31}P-NMR spectroscopy indicated a singlet for a phosphate group at approximately -3.5 ppm in each case. The obtained products resulted from nucleophilic attack of dibenzyl hydrogen phosphate at C-3 of the *N*-acyl aziridine derivatives **34**, **35**, and **36**. These observations were also confirmed by detailed analyses of ^{1}H, ^{13}C-NMR spectra, and (H,H)-COSY experiments of compounds **37**, **38** and **39**. The position of the amide functionality in the structures of **37**, **38**, and **39** could easily be deduced from the ^{1}H-NMR spectra of the obtained products, irradiated at δ = 4.07 ppm (H-2). The splitting patterns the of proton in the amide function (δ = 6.74 ppm), as well as H-3 (δ = 3.45-3.40 ppm) and H-1 (δ = 3.63-3.61 ppm) were affected. The signal assigned to a proton in the amide function (doublet,

δ = 6.7 ppm) changed to a singlet after irradiation at δ = 4.06 ppm (H-2). The signals for H-1 and H-3 were each transformed from a doublet-doublet (dd) into a doublet (d). The position of the amide functionality at C-2 was also confirmed by (H,H)-COSY spectra which indicated the coupling between the proton in the amide function and H-2.

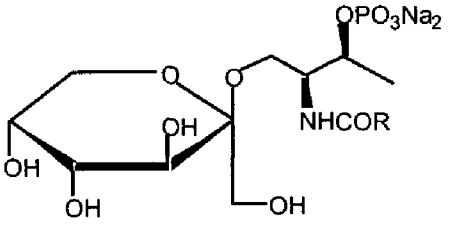
The final products in the sequence of reactions were obtained by catalytic hydrogenolysis of **37**, **38**, and **39** in the presence of palladium on carbon (10%), and the resultant products were subsequently converted into the corresponding disodium salt **40**, **41**, and **42** using ion exchange resin (Dowex-50Wx2, sodium form).



34 R =$C_{11}H_{23}$ (72.2%)
35 R =$C_{13}H_{27}$ (69.9%)
36 R =$C_{15}H_{31}$ (87.2%)



37 R =$C_{11}H_{23}$ (72.3%)
38 R =$C_{13}H_{27}$ (69.9%)
39 R =$C_{15}H_{31}$ (75.0%)



40 R =$C_{11}H_{23}$ (70.8%)
41 R =$C_{13}H_{27}$ (72..4%)
42 R =$C_{15}H_{31}$ (69.2%)

6.3 Concluding remarks

The results presented above, allow the conclusion that the catalytic asymmetric dihydroxylation reaction of perbenzylated but-2-enyl fructopyranoside **6** is highly stereoselective. It has also been demonstrated that the nucleophilic ring-opening of the cyclic sulfate by azide ion, and *N*-acyl aziridine derivatives by dibenzyl hydrogen phosphate, proceeds with inversion of stereochemistry at the respective chiral carbons. The activation of the aziridine group by *N*-acylation makes the aziridine ring more susceptible to ring-opening. In all cases, the nucleophilic attack on the *N*-acyl aziridine derivatives by dibenzyl phosphate resulted in the formation of a single product, by a selective attack at C_3 of the aglycon moiety.

6.4 Experimental section

General experimental procedures are given in Chapter 3.

But-2-enyl β-**D**-*fructopyranoside (4)*

D-Fructose **2** (10.0 g, 55.55 mmol) was added to a stirred mixture of crotyl alcohol (50 mL) and acetyl chloride (1.5 mL) and then set aside at room temperature for 48 hr. The solid material was collected by filtration washed with ethanol and ether. Crystallization of the crude material from ethanol containing a few drops of 25% aqueous ammonia solution gave **4** (8.56 g, 65.8%). m.p. 179-180°C; $[\alpha]_D$ –148° (MeOH) MS (FAB-Na^+) M/z 257 (M^++ Na^+), ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 131.72 (-OCH_2*C*H=CH_2CH_3), 127.83 (-OCH_2CH=*C*H_2CH_3), 102.06 (C-2), 70.85 (C-3), 70.37 (C-4), 69.4 (C-5), 65.17 (C-1), 63.00 (C-1'), 62.57 (C-6), and 18.28 (*C*H_3) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 4.0-3.90 (m, 3H, H-2', H-3', H-3), 3.89-3.84 (m, 2H, H-4, H-5), 3.79-3.65 (m, 6H, H-1, H-1', H-6) ppm. *Anal* calc for $C_{10}H_{18}O_6$: C 51.27; H 7.75. Found: C 50.95; H 7.68%.

The original filtrate, not mixed with the washings, was reacted with **2** (10.0 g, 55.55 mmol) to give a further crop of **4** (1.3 g, 10%).

But-2-enyl 1,3,4,5-tetra-O-*benzyl*-β-**D**-*fructopyranoside (6)*

A cooled (0°C) mixture of but-2-enyl β-**D**-fructopyranoside (**4**) (5.0 g, 21.37 mmol) in dimethyl sulfoxide (50 mL) containing powdered potassium hydroxide (5.98 g, 106.85 mmol, 5 eq) was subjected to benzyl chloride (12.2 mL, 106.85 mmol, 5 eq). The reaction was stirred at room temperature for *ca* 24 hr. The reaction mixture was diluted with ether (100 mL) and water (40 mL). The aqueous layer separated from organic layer was treated with ether (50 mL). The combined organic layer was washed with saturated sodium chloride (3x20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Column chromatography (n-hexane-ethyl acetate, 3:1) of the crude material gave compound **6** (11.2 g, 88.4%) as colourless oil. $[\alpha]_D$ –50.5° ($CHCl_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 138.91, 138.72, 138.55, 138.01, 128.20, 128.14, 128.00, 127.95, 127.68, 127.67, 127.57, 127.35, 127.21 (aromatic-C), 131.82 (-OCH_2*C*H=CH_2CH_3), 127.88 (-OCH_2CH=*C*H_2CH_3), 101.79 (C-2), 78.87 (C-3), 76.25 (C-4), 75.49 (benzylic-C), 73.66 (C-5), 73.43, 72.19, 71.07 (benzylic-C), 70.23 (C-1), 62.00 (C-1'), 61.05 (C-6), and 17.68 (*C*H_3) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.42-7.21 (m, 20H, aromatic H), 5.68-5.47 (m, 2H, H-2', H-3'), 4.93, 4.62 (2d, 2H, J = 11.3 Hz, benzylic-H), 4.77, 4.74 (2d, 2H, J = 12.6 Hz, benzylic-H), 4.68, 4.40 (2d, 2H, J = 11.9 Hz, benzylic-H), 4.36 (d, 1H, H-3), 4.0-3.93 (m, 3H, H-1'a, H-1'b, H-4), 3.87 (dd, 1H, $J_{5,6eq}$ = 1.8 Hz, $J_{6ax,6eq}$ = -11.9 Hz, H-6eq), 3.83 (m, 1H, H-5), 3.77 (d, 1H, J = -10.1 Hz, H-1a), 3.62 (d, 1H, J = -10.1 Hz, H-1b), 3.55 (dd, 1H, $J_{5,6ax}$ = 1.4 Hz, $J_{6ax,6eq}$ = -11.9 Hz, 6ax).ppm.

n-Butyl β-**D**-*fructopyranoside (7)*

A solution of compound **4** (500 mg, 2.136 mmol) in water (30 mL) containing 1 drop of triethylamine and palladized charcoal (5%, 80 mg) was hydrogenated at room temperature for 6 hr. The inorganic material was removed by filtration, washed with water and the combined filtrate and washings concentrated *in vacuo* to give **7** (450 mg, 89%), m.p 156-158°C (ethanol), $[\alpha]_D$ –146° (MeOH), Lit[1] m.p. 156-158°C, (ethanol), $[\alpha]_D$ –145° (MeOH).

*2(**R**),3(**R**)-Dihydroxybutyl 1',3',4',5'-tetra-*O*-benzyl β-**D**-fructopyranoside (**8**)*

A mixture of $(DHQD)_2$.PHAL (77 mg), $K_2OsO_2(OH)_4$ (14.49 mg), K_2CO_3 (4.04 g), $K_3Fe(CN)_6$ (9.75 g), and methanesulfonamide (941.3 mg) in water (50 mL) was added to a solution of **6** (5.9 g, 9.9 mmol) in *t*-butyl alcohol (50 mL). The reaction mixture was stirred vigorously at room temperature for *ca* 4 hr. The reaction was quenched by addition of Na_2SO_3 (15 g) and stirred for 1 hr. The reaction mixture was diluted with ether (100 mL) and water (60 mL). The aqueous layer was washed with ether (2x50 mL). The combined organic layer was then washed with saturated sodium chloride (40 mL), potassium hydroxide (2N, 20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Crystallization of the crude material from di-isopropyl ether gave compound **8** (5.1 g, 82%) as white crystals. m.p. 134-135°C; $[\alpha]_D$ –52.5° ($CHCl_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 138.51, 138.37, 138.33, 137.70, 128.31, 128.19, 127.87, 127.85, 127.76, 127.67, 127.64, 127.55, 127.53, 127.46 (aromatic-C), 100.97 (C-2), 78.75 (C-3), 76.66 (C-4), 75.50, 73.64 (benzylic-C), 73.30 (C-5), 73.13 (C-2'), 72.19, 71.24 (benzylic-C), 70.26 (C-1'), 68.51 (C-3'), 64.87 (C-1), 61.21 (C-6), 19.58 (*C*H_3) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.40-7.20 (m, 20H, aromatic H), 4.90, 4.60 (2d, 2H, J = 11.0 Hz, benzylic-H), 4.73, 4.65 (2d, 2H, J = 12.6 Hz, benzylic-H), 4.62, 4.44 (2d, 2H, J = 11.9 Hz, benzylic-H), 4.30 (d, 1H, J = 9.9 Hz, H-3), 3.89 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.18 Hz, H-4), 3.88 (dd, 1H, $J_{5,6eq}$ = 1.8 Hz, $J_{6ax,6eq}$ = -12.3 Hz, H-6eq), 3.85 (dd, 1H, $J_{5,6ax}$ = 1.6 Hz, $J_{6ax,6eq}$ = -12.3 Hz, H-6ax), 3.80 (m, 1H, H-2'), 3.78 (m, 1H, H-5) 3.76 (d, 1H, J = -10.2 Hz, H-1a), 3.65 (d, 1H, J = -10.2 Hz, H-1b), 3.62-3.37 (m, 3H, H-1'a, H-1'b, H-3'), 2.97, 1.82 (bs, OH), 1.17 (d, 3H, $J_{3',4'}$ = 6.4 Hz, CH_3) ppm. *Anal* calc for $C_{38}H_{44}O_8$: C 72.59; H 7.05. Found: C 72.47; H 7.06%.

In a similar manner treatment of compound **6** (2.95 g, 4.95 mmol) with a mixture of $(DHQ)_2$PHAL (38.5 mg), $K_2OsO_2(OH)_4$ (7.25 mg), K_2CO_3 (2.02 g), $K_3Fe(CN)_6$ (4.87 g) and methanesulfonamide (471 mg) in 50% aqueous *tert*-butyl alcohol (100 ml) at room temperature for 4 h. gave compound **8** (2.736 g, 88%), m.p. 134-136°C, $[\alpha]_D$ -52°. The spectral data was identical to that reported above.

*2(**R**),3(**R**)-Dibenzoxybutyl 1',3',4',5'-tetra-*O*-benzyl-β-**D**-fructopyranoside (**10**)*

A sample of compound **8** (1.0g, 1.59 mmol) in dimethyl sulfoxide (10 mL) containing powdered potassium hydroxide (178 mg, 3.18 mmol, 2 eq) was benzylated in the usual manner using benzyl chloride (0.35 mL, 3.18 mmol, 2 eq) to give compound **10** (1.1 g, 87%) as a pure colourless oil. $[\alpha]_D$ –58.4° ($CHCl_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 138.51, 138.37, 138.33, 137.70, 128.31, 128.19, 127.87, 127.85, 127.76, 127.67, 127.64, 127.55, 127.53, 127.46 (aromatic-C), 100.97 (C-2), 78.75 (C-3), 76.66 (C-4), 75.50, 73.64 (benzylic-C), 73.30 (C-5), 73.13 (C-2'), 72.6, 72.9, 72.19, 71.24 (benzylic-C), 70.26 (C-1'), 68.51 (C-3'), 64.87 (C-1), 61.21 (C-6), 19.58 (*C*H_3) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.43-7.20 (m, 30H, aromatic H), 4.98, 4.60 (d, 1H, J = 11.4 Hz, benzylic-H), 4.77, 4.72 (2d, 2H, J = 12.8 Hz, benzylic-H), 4.68-4.56 (m, 8H, benzylic-H), 4.45 (1d, 1H, J = 11.9 Hz, benzylic-H), 4.35 (d, 1H, J = 10.1 Hz, H-3), 3.96, 3.91 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.2 Hz, H-4), 3.85-3.53 (m, 9H, H-1a, H-1b, H-1'a, H-1'b, H-2', H-3', H-5, H-6eq, H-6ax), 1.18 (d, 3H, $J_{3',4'}$ = 6.4 Hz, CH_3) ppm.

*1-Deoxy-***D***-threitol 2,3,4-tris-p-nitrobenzoate (13)*

Compound **10** (1.0 g, 1.24 mmol) was treated at room temperature with a mixture of trifluoroacetic acid / water (9:1) (5 mL) for 10 mins. The resultant reaction mixture was concentrated *in vacuo*. Column chromatography of the crude material (hexane - ethylacetate, 9:2) gave **11** (259 mg, 73%). The material obtained was then subjected to hydrogenolysis in the presence of palladium on charcoal (10%, 60 mg) for 2 hr. The catalyst was removed by filtration, washed with methanol and the combined filtrate and washings concentrated *in vacuo* to yield compound **12** as a colourless oil (89 mg, 92.6%). *p*-Nitrobenzoyl chloride (662.5 mg, 3.35 mmol, 4 eq) was then added to a cooled (0°C) solution of **12** in dry pyridine (5 mL). The reaction was kept aside at room temperature for 3 days. The mixture was concentrated *in vacuo*, and the residue obtained was crystallized ($CHCl_3$ / MeOH) to give **13** (236 mg, 51%) as yellowish crystals. m.p. 130-131°C: $[\alpha]_D$ –9.0° ($CHCl_3$); (lit [14-15] m.p. 129-131°C $[\alpha]_D$ –9.05° ($CHCl_3$), {*Cf.* lit [16] (erythro isomer) m.p. 159-160°C; $[a]_D$ 81.07° ($CHCl_3$)}. Anal. Calc. for $C_{25}H_{19}O_{12}N_3$: C 54.26; H 3.46; N 7.59. Found: C 54.33; H 3.29; N 7.54%.

Continued elution (dichloromethane - methanol, 100:1) gave an anomeric mixture of 1,3,4,5-tetra-*O*-benzylfructopyranose (see chapter 3).

*2(***R***),3(***R***)-Dihydroxybutyl-1',3',4',5'-tetra-*O*-benzyl-β-***D***-fructopyranoside-2,3-*O*-cyclic sulfate (15)*

A stirred, cooled (0°C) solution of compound **8** (1.3 g, 2.07 mmol) in dichloromethane (10 mL) containing triethylamine (0.7 mL) was treated dropwise with a solution of thionyl chloride (0.27 mL, 3.72 mmol, 1.8 eq) in dichloromethane (3 mL) for 10 mins, and then set aside for more 10 mins. The mixture was treated with dichloromethane (50 mL), washed with water (2x25 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resultant crude product in a mixture of CCl_4 / CH_3CN / H_2O (1:1:1, 15 mL) was treated with sodium periodate (615 mg, 2.87 mmol, 1.39 eq) and $RuCl_3.xH_2O$ (2 mg) at room temperature for 1 hr. The mixture was then diluted with ether (40 mL), washed with water (2x10 mL), saturated aqueous $NaHCO_3$ (2x10 mL), saturated aqueous sodium chloride (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (n-hexane-ethyl acetate 1:1) of the crude material gave cyclic sulfate **15** (1.143 g, 80%) as a pure colourless oil. $[\alpha]_D$ –47.7° ($CHCl_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 138.86, 138.42, 138.38, 137.56, 128.32, 128.25, 128.22, 128.14, 128.08, 128.04, 127.92, 127.88, 127.85, 127.79, 127.67, 127.65, 127.53, 127.46, 127.43, 127.29 (aromatic-C), 101.47 (C-2), 79.89 (C-3), 78.28 (C-4), 76.55, 76.43, 75.08 (benzylic-C), 73.74 (C-5), 73.45 (C-2'), 72.13 (benzylic-C), 71.39 (C-1'), 70.80 (C-1), 61.58 (C-6), 58.17 (C-3'), 17.16 (*C*H_3) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.39-7.21 (m, 20H, aromatic H), 4.93 (d, 1H, J = 11.4 Hz, benzylic-H), 4.76, 4.71 (2d, 2H, J = 12.6 Hz, benzylic-H), 4.61- 4.53 (m, 4H, benzylic-H), 4.49 (d, 1H, J = 11.8 Hz, benzylic-H), 4.22 (d, 1H, J = 10.0 Hz, H-3), 4.07, 3.99 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.2 Hz, H-4), 3.84 (m, 1H, H-5), 3.74 (dd, 1H, J = 4.4 Hz, H-1'a), 3.74-3.64 (m, 5H, H-1'b, H-1a, H-1b, H-3'a, H-3'b), 1.29 (d, 3H, J = 6.3 Hz, C*H*$_3$) ppm.

*2(***R***)-Hydroxy,3(***S***)-azidobutyl 1',3',4',5'-tetra-*O*-benzyl-β-***D***-fructopyranoside (17a)*

A stirred solution of **15** (1.143 g, 1.66 mmol) in DMF (5 mL) was treated with lithium azide (149.4 mg, 3.32 mmol, 2.0 eq) at 80°C for 1 hr. The mixture was concentrated *in vacuo*,

dissolved in freshly distilled tetrahydrofuran (10 mL), cooled (0°C) and a few drops of concentrated H_2SO_4 were added and then stirred at room temperature for 15 mins. The reaction was completed (TLC) and saturated aqueous sodium hydrogen carbonate (10 mL) solution was added to neutralize the acid, the mixture was stirred for an extra 15 mins, and treated with ether (20 mL). The separated organic layer was washed with 10% sodium chloride solution (20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Column chromatography (n-hexane-ethyl acetate, 1:1) of the crude product gave compound **17a** as a colourless oil (763 mg, 70%). $[\alpha]_D$ –42.2° ($CHCl_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 138.47, 138.44, 138.39, 137.73, 128.36, 128.30, 128.24, 128.22, 128.11, 128.05, 127.93, 127.74, 127.64, 127.55, 127.52 (aromatic-C), 101.48 (C-2), 78.58 (C-3), 76.71 (C-4), 75.62, 73.71 (benzylic-C), 73.46 (C-5), 73.33 (C-2'), 72.07, 71.35 (benzylic-C), 70.21 (C-1'), 63.11 (C-1), 61.39 (C-6), 58.69 (C-3'), 15.30 (*C*H$_3$) ppm. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.40-7.19 (m, 20H, aromatic H), 4.88, 4.60 (2d, 2H, J = 10.8 Hz, benzylic-H), 4.76, 4.70(2d, 2H, J = 12.5 Hz, benzylic-H), 4.66, 4.45 (2d, 2H, J = 11.8 Hz, benzylic-H), 4.32 (d, 1H, J = 10.0 Hz, H-3), 3.92 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.18 Hz, H-4), 3.88 (dd, 1H, $J_{5,6eq}$ = 1.8 Hz, $J_{6ax,6eq}$ = -12.3 Hz, H-6eq), 3.85 (dd, 1H, $J_{5,6ax}$ = 1.6 Hz, $J_{6ax,6eq}$ = -12.3 Hz, H-6ax), 3.81 (m, 1H, H-2'), 3.79 (m, 1H, H-5) 3.77 (d, 1H, J = -10.32 Hz, H-1a), 3.64 (d, 1H, J = -10.32 Hz, H-1b), 3.58-3.44(m, 3H, H-1'a, H-1'b, H-3'), 1.28 (d, 3H, $J_{3',4'}$ = 6.4 Hz, C*H*$_3$) ppm.

*2(**R**)-Hydroxy,3(**S**)-aminobuty- 1',3',4',5'-tetra*-O-*benzyl*-β-**D**-*fructopyranoside (**19**)*

A stirred solution of **17a** (652 mg, 0.99 mmol) in pyridine (10 mL) was treated with triphenylphosphine (376 mg, 1.98 mmol, 2.0 eq) at room temperature until evolution of nitrogen ceased. Ammonium solution (25%, 2 mL) was then added and the mixture was set aside for 12 hr. The mixture was concentrated *in vacuo* and column chromatography (CH_2Cl_2-MeOH, 9:1) of the residue gave **19** (466.8 mg, 74.5 %) as a colourless oil. $[\alpha]_D$ –57.0° ($CHCl_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 132.06, 131.93, 131.86, 128.49, 128.33, 128.21, 128.17, 128.11, 128.06, 128.02, 127.99, 127.70, 127.57, 127.41, 127.39, 127.31, 127.26 (aromatic-C), 101.36 (C-2), 78.59 (C-3), 76.30 (C-4), 75.45, 73.49 (benzylic-C), 73.46 (C-5), 73.33 (C-2'), 72.07, 71.35 (benzylic-C), 70.21 (C-1'), 63.11 (C-1), 61.39 (C-6), 58.69 (C-3'), 15.30 (*C*H$_3$) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.40-7.19 (m, 20H, aromatic H), 4.88, 4.60 (2d, 2H, J = 10.8 Hz, benzylic-H), 4.76, 4.70 (2d, 2H, J = 12.5 Hz, benzylic-H), 4.66, 4.45 (2d, 2H, J = 11.8 Hz, benzylic-H), 4.32 (d, 1H, J = 10.0 Hz, H-3), 3.92 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.18 Hz, H-4), 3.88 (dd, 1H, $J_{5,6eq}$ = 1.8 Hz, $J_{6ax,6eq}$ = -12.3 Hz, H-6eq), 3.85 (dd, 1H, $J_{5,6ax}$ = 1.6 Hz, $J_{6ax,6eq}$ = -12.3 Hz, H-6ax), 3.81 (m, 1H, H-2'), 3.79 (m, 1H, H-5) 3.77 (d, 1H, J = -10.32 Hz, H-1a), 3.64 (d, 1H, J = -10.32 Hz, H-1b), 3.58-3.44 (m, 3H, H-1'a, H-1'b, H-3'), 1.28 (d, 3H, $J_{3',4'}$ = 6.4 Hz, C*H*$_3$) ppm.

*2(**R**)-p-Toluenesulfonoxy,3(**S**)-azidobutyl-1',3',4',5'-tetra*-O-*benzyl*-β-**D**-*fructopyranoside (**20**)*

A stirred, cooled (0°C) solution of compound **17a** (763 mg, 1.17 mmol) in dry pyridine (5 mL) was treated with *p*-toluenesulfonyl chloride (782 mg, 4.09 mmol, 3.5 eq) and set aside at room temperature for 24 hr. The reaction mixture was treated with ice water and left for 1 hr, diluted with dichloromethane (50 mL) and washed successively with aqueous hydrochloric acid (2**M**, 20 mL), water (20 mL) and a solution of saturated sodium hydrogen carbonate (20 mL). The organic extract was dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (n-

hexane-ethyl acetate, 3:1) of the crude material gave **20** (759 mg, 80%) as a colourless oil. $[\alpha]_D$ –34.1° ($CHCl_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 139.06, 138.50, 138.42, 137.80, 129.82, 129.72, 129.66, 128.30, 128.25, 128.19, 128.07, 127.90, 127.77, 127.69, 127.57, 12751, 127.49, 127.40, 127.27, 127.21 (aromatic-C), 101.76 (C-2), 78.24 (C-3), 76.57 (C-4), 76.21, 75.28 (benzylic-C), 73.60 (C-5), 73.49 (C-2'), 72.09, 71.18 (benzylic-C), 70.13 (C-1'), 64.73 (C-1), 61.34 (C-6), 59.80 (C-3'), and 21.53, 15.43 (*C*H_3) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.79-7.07 (m, 24H, aromatic H), 4.93, 4.60 (2d, 2H, J = 11.2 Hz, benzylic-H), 4.76, 4.70 (2d, 2H, J = 12.6 Hz, benzylic-H), 4.66, 4.43 (2d, 2H, J = 11.9 Hz, benzylic-H), 4.32 (d, 1H, J = 10.1 Hz, H-3), 4.0, 3.97 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.1 Hz, H-4), 3.88-3.57 (m, 9H, H-1a, H-1b, H-1'a, H-1'b, H-2', H-3', H-5, H-6eq, H-6ax,), 2.32 (s, 3H, CH_3), 1.17 (d, 3H, $J_{3',4'}$ = 6.4 Hz, C*H*$_3$) ppm.

*2(**S**),3(**S**)-Aziridinobutyl-1',3',4',5'-tetra*-O-*benzyl*-β-**D**-*fructopyranoside (21)*

A stirred cooled (0°C) solution of **20** (759 mg, 0.94 mmol) in freshly distilled tetrahydrofuran (10 mL) was treated with lithium aluminium hydride (160 mg, 4.23 mmol, 4.5 eq). The reaction mixture was stirred at room temperature for 45 mins. The reaction was quenched by addition of ether (20 mL) and water (0.5 mL), filtered over $MgSO_4$, and concentrated *in vacuo*. Column chromatography (dichloromethane-methanol 9:1) of the crude product gave **21** (394 mg, 69%) as a pure colourless oil. $[\alpha]_D$ –59.1° ($CHCl_3$); MS (CI-CH_4) M/z 610 (M^++H), 540 (M^++H–C_3H_8N). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 138.83, 138.62, 138.46, 137.93, 128.31, 128.26, 128.23, 128.17, 128.11, 128.08, 128.05, 127.76, 127.72, 127.69, 127.66, 127.63, 127.57, 127.47, 127.44, 127.32 (aromatic-C), 101.41 (C-2), 78.64 (C-3), 76.35 (C-4), 75.51 (benzylic-C), 73.54 (C-5), 72.14, 72.07, 70.25 (benzylic-C), 70.25 (C-1'), 63.21 (C-1), 61.04 (C-6), 37.53 (C-2'), 30.27 (C-3'), 18.99 (*C*H_3) ppm. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.40-7.23 (m, 20H, aromatic H), 4.93, 4.60 (2d, 2H, J = 11.2 Hz, benzylic-H), 4.74, 4.65 (2d, 2H, J = 12.6 Hz, benzylic-H), 4.64, 4.42 (2d, 2H, J = 11.9 Hz, benzylic-H), 4.34 (d, 1H, J = 10.1 Hz, H-3), 4.00 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.19 Hz, H-4), 3.83 (dd, 1H, $J_{5,6eq}$ = 1.89 Hz, $J_{6ax,6eq}$ = -12.3 Hz, H-6eq), 3.80 (dd, 1H, $J_{5,6ax}$ = 1.87 Hz, $J_{6ax,6eq}$ = -12.3 Hz, H-6ax), 3.79 (m, 1H, H-5), 3.74 (d, 1H, J = -10.1 Hz, H-1a), 3.60 (d, 1H, J = -10.1 Hz, H-1b), 3.64 (dd, 1H, J = 6.37 Hz, H-1'a), 3.39 (dd, 1H, J = 6.37 Hz, H-1'b), 1.90 (m, 1H, H-2'), 1.74 (m, 1H, H-3'), 1.19 (d, 3H, $J_{3',4'}$ = 5.5 Hz, C*H*$_3$) ppm.

*2(**R**)-Hydroxy,3(**S**)-dodecanoylamidobutyl-1',3',4',5'-tetra*-O-*benzyl*-β-**D**-*fructopyranoside (22)*

A stirred, cooled (0°C) solution of compound **19** (188 mg 0.299 mmol) in dichloromethane (10 mL) containing triethylamine (0.1 mL, 2.5 eq) was treated with lauroyl chloride (0.1 mL, 0.329 mmol, 1.1 eq) for 30 mins. The mixture was then diluted with dichloromethane (20 mL) and washed, successively with aqueous hydrochloric acid (2**M**, 20 mL), water (20 mL) and a solution of saturated sodium hydrogen carbonate (20 mL). The organic extract was dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (n-hexane-ethyl acetate, 1:1) of the crude material gave **22** (299.6 mg, 70%) as a colourless oil. $[\alpha]_D$ –70.7° ($CHCl_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 173.86 (*C*=O), 138.42, 138.29, 138.24, 137.56, 133.00, 129.84, 129.71, 129.61, 128.45, 128.38, 128.31, 128.19, 128.01, 128.02, 127.77, 127.71, 127.66, 127.59, 127.49 (aromatic-C), 100.58 (C-2), 79.55 (C-3), 77.95 (C-4), 75.82,

73.76 (benzylic-C), 73.70 (C-5), 71.98, 71.87 (benzylic-C), 71.77 (C-1'), 70.45 (C-2'), 62.52 (C-1), 60.77 (C-6), 47.49 (C-3'), 36.48 ($COCH_2$), 29.58-22.65 (aliphatic C), and 16.62, 14.1 (CH_3) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.39-7.18 (m, 20H, aromatic H), 6.50 (d, 1H, J = 9.33 Hz N*H*CO), 4.87, 4.62 (2d, 2H, J = 10.5 Hz, benzylic-H), 4.76, 4.69 (2d, 2H, J = 12.4 Hz, benzylic-H), 4.56, 4.48 (2d, 2H, J = 11.7 Hz, benzylic-H), 4.31(d, 1H, J = 9.5 Hz, H-3), 3.90-3.80 (m, 4H, H-1a, H-4, H-5, H-6eq), 3.74-3.57 (m, 5H, H-1b, H-1'a, H-1'b, H-2', H-6ax), 1.90 (bs, 1H, OH), 1.14-1.13 (m, 21H, aliphatic H), 1.07 (d, 3H, J = 6.9 Hz, C*H*$_3$-butyl), and 0.87 (t, 3H, J = 6.8 Hz, C*H*$_3$) ppm.

*2(**R**)-Hydroxy,3(**S**)-tetradecanoylamidobutyl-1',3',4',5'-tetra-*O*-benzyl-β-**D**-fructopyranoside (23)*

Compound **23** was synthesized by treatment of **19** (184 mg, 0.293 mmol) with myristoyl chloride (0.1 mL, 0.322 mmol, 1.1 eq), using the same procedure as described for the synthesis of compound **22**. Column chromatography (n-hexane-ethyl acetate, 1:1) of the crude material gave **23** (195.7 mg, 79%) as a colourless oil. $[\alpha]_D$ – 71.6° ($CHCl_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 173.84 (*C*=O), 138.40, 138.30, 138.24, 137.56, 133.10, 129.82, 129.61, 128.44, 128.27, 128.15, 128.01, 127.75, 127.69, 127.65, 127.59, 127.39 (aromatic-C), 100.70 (C-2), 79.44 (C-3), 77.75 (C-4), 75.85, 73.73 (benzylic-C), 73.72 (C-5), 72.01, 71.84 (benzylic-C), 71.76 (C-1'), 70.44 (C-2'), 62.51 (C-1), 60.76 (C-6), 47.47 (C-3'), 36.45 ($COCH_2$), 29.56-22.64 (aliphatic C), and 16.62, 14.1 (CH_3) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.39-7.21 (m, 20H, aromatic H), 6.60 (d, 1H, J = 9.33 Hz, N*H*CO), 4.89, 4.63 (2d, 2H, J = 10.5 Hz, benzylic-H), 4.75, 4.68 (2d, 2H, J = 12.5 Hz, benzylic-H), 4.56, 4.48(2d, 2H, J = 11.8 Hz, benzylic-H), 4.29(d, 1H, J = 9.7 Hz, H-3), 3.87-3.80 (m, 4H, H-1a, H-4, H-5, H-6eq), 3.77-3.61 (m, 5H, H-1b, H-1'a, H-1'b, H-2', H-6ax), 1.25 (m, 24H, aliphatic H), 1.07 (d, 3H, J = 6.9 Hz, C*H*$_3$-butyl), and 0.87 (t, 3H, J = 6.8 Hz, C*H*$_3$) ppm.

*2(**R**)-Hydroxy,3(**S**)-hexadecanoylamidobutyl-1',3',4',5'-tetra-*O*-benzyl-β-**D**-fructopyranoside (24)*

Compound **24** was synthesized by treatment of **19** (264 mg, 0.421 mmol) with palmitoyl chloride (0.1 mL, 0.463 mmol, 1.1 eq), using the same procedure as described for the synthesis of compound **22**. Column chromatography (n-hexane-ethyl acetate, 1:1) of the crude material gave **24** (262.5 mg, 72%) as a colourless oil. $[\alpha]_D$ –71.0° ($CHCl_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 173.83 (*C*=O), 138.41, 138.32, 138.25, 137.54, 133.12, 129.85, 129.59, 128.42, 128.26, 128.17, 128.03, 127.76, 127.67, 127.64, 127.57, 127.49 (aromatic-C), 100.72 (C-2), 79.43 (C-3), 77.76 (C-4), 75.84, 73.72 (benzylic-C), 73.73 (C-5), 72.02, 71.85 (benzylic-C), 71.74 (C-1'), 70.45 (C-2'), 62.52 (C-1), 60.73 (C-6), 47.44 (C-3'), 36.43 ($COCH_2$), 29.57-22.63 (aliphatic C), and 16.61, 14.11 (CH_3) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.39-7.19 (m, 20H, aromatic H), 6.50 (d, 1H, J = 9.33 Hz, N*H*CO), 4.89, 4.64 (2d, 2H, J = 10.5 Hz, benzylic-H), 4.76, 4.69 (2d, 2H, J = 12.5 Hz, benzylic-H), 4.55, 4.48 (2d, 2H, J = 11.8 Hz, benzylic-H), 4.29 (d, 1H, J = 9.7 Hz, 3), 3.87-3.80(m, 4H, H-1a, H-4, H-5, H-6eq), 3.77-3.60 (m, 5H, H-1b, H-1'a, H-1'b, H-2', H-6ax), 1.25 (m, 28H, aliphatic H), 1.07 (d, 3H, J = 6.9 Hz, C*H*$_3$-butyl), and 0.87 (t, 3H, J = 6.8 Hz, C*H*$_3$) ppm.

*2(**R**)-Dodecanoxy,3(**S**)-dodecanoylamidobutyl-1',3',4',5'-tetra-*O*-benzyl-β-**D**-fructopyranoside (25)*

A stirred cooled (0°C) solution of **22** (234 mg, 0.289 mmol) in dry pyridine (5 mL) was treated with lauroyl chloride (0.1 mL, 0.318 mmol, 1.1 eq). The reaction was set aside at room temperature for 1 hr. The mixture was treated with ice water (1 hr), diluted with dichloromethane (20 mL) and washed, successively with aqueous hydrochloric acid (2**M**, 20 mL), water (20 mL) and a solution of saturated sodium hydrogen carbonate (20 mL). The organic extract was dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (n-hexane-ethyl acetate, 1:1) of the crude material gave **25** (219.6 mg, 76%) as a colourless oil. $[\alpha]_D$ –69.0° ($CHCl_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 172.92, 172.76 (*C*=O), 138.39, 138.19, 137.44, 134.43, 133.26, 130.02, 129.71, 128.96, 128.47, 128.34, 128.18, 128.04, 127.95, 127.77, 127.72, 127.66, 127.59, 127.38, 126.88 (aromatic-C), 100.65 (C-2), 79.76 (C-3), 77.42 (C-4), 75.68, 73.79 (benzylic-C), 73.42 (C-5), 72.31, 72.11 (benzylic-C), 71.17 (C-1'), 70.38 (C-2'), 60.79 (C-1), 60.50 (C-6), 45.29 (C-3'), 36.93 ($COCH_2$), 34.33-22.65 (aliphatic C), and 17.32, 14.08 (CH_3) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.37-7.23 (m, 20H, aromatic H), 6.91 (d, 1H, J = 9.33 Hz, N*H*CO), 4.89, 4.62 (2d, 2H, J = 10.7 Hz, benzylic-H), 4.77, 4.69 (2d, 2H, J = 12.6 Hz, benzylic-H), 4.56, 4.49 (2d, 2H, J = 11.7 Hz, benzylic-H), 4.29 (d, 1H, J = 9.6 Hz, H-3), 3.86-3.49 (m, 9H, H-1a, H-1b, H-1'a, H-1'b, H-2', H-4, H-5, H-6ax, H-6eq), 2.35-2.18 (m, 4H, $COCH_2$), 1.62-1.22 (m, 36H, aliphatic H), 1.11 (d, 3H, J = 6.9 Hz, CH_3-butyl), and 0.88 (2xt, 3H, 2xCH_3) ppm.

*2(**R**)-Tetradecanoxy,3(**S**)-tetradecanoylamidobutyl-1',3',4',5'-tetra-*O*-benzyl-β-**D**-fructopyranoside (26)*

Compound **23** (195.7 mg, 0.233 mmol) was treated with myristoyl chloride (0.1 mL, 0.256 mmol, 1.1 eq) under the same conditions used to prepare compound **25**. Column chromatography (n-hexane-ethyl acetate, 1:1) of the crude product gave **26** (177.5 mg, 72.5%) as a colourless oil. $[\alpha]_D$ –73.8° ($CHCl_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 172.86, 172.74 (*C*=O), 138.47, 138.24, 137.47, 133.38, 130.05, 129.74, 128.99, 128.34, 128.18, 128.02, 127.94, 127.70, 127.63, 127.47, 126.75 (aromatic-C), 100.70 (C-2), 79.77 (C-3), 78.26 (C-4), 75.72, 73.80 (benzylic-C), 73.13 (C-5), 72.32, 72.17 (benzylic-C), 71.25 (C-1'), 70.48 (C-2'), 60.84 (C-1), 60.48 (C-6), 45.64 (C-3'), 36.43 ($COCH_2$), 34.36-22.67 (aliphatic C), and 17.36, 14.11 (CH_3) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.39-7.22 (m, 20H, aromatic H), 6.90 (d, 1H, J = 9.33 Hz, N*H*CO), 4.89, 4.64 (2d, 2H, J = 10.7 Hz, benzylic-H), 4.74, 4.68(2d, 2H, J = 12.6 Hz, benzylic-H), 4.58, 4.48 (2d, 2H, J = 11.8 Hz, benzylic-H), 4.30 (d, 1H, J = 9.7 Hz, H-3), 3.86-3.48 (m, 9H, H-1a, H-1b, H-1'a, H-1'b, H-2', H-4, H-5, H-6ax, H-6eq), 2.23-2.20 (m, 4H, $COCH_2$), 1.60-1.25 (m, 44H, aliphatic H), 1.11 (d, 3H, J = 6.9 Hz, CH_3-butyl), and 0.88 (2xt, 6H, 2xCH_3) ppm.

*2(**R**)-Hexadecanoxy,3(**S**)-hexadecanoylamidobutyl-1',3',4',5'-tetra-*O*-benzyl-β-**D**-fructopyranoside (27)*

Compound **27** (122mg, 0.141 mmol) was treated with palmitoyl chloride (0.1 mL, 0.155 mmol, 1.1 eq) by the same procedure used to prepare compound **25**. Column chromatography (n-hexane-ethyl acetate, 1:1) of the crude product gave **27** (126.2 mg, 81%) as a colourless oil.

$[\alpha]_D$ – 68.3° ($CHCl_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 172.87, 172.76 (*C*=O), 138.45, 138.25, 137.49, 133.35, 130.08, 129.73, 128.98, 128.36, 128.19, 128.05, 127.95, 127.73, 127.61, 127.41, 126.79 (aromatic-C), 100.69 (C-2), 79.79 (C-3), 78.27 (C-4), 75.73, 73.81 (benzylic-C), 73.11 (C-5), 72.35, 72.16 (benzylic-C), 71.22 (C-1'), 70.46 (C-2'), 60.85 (C-1), 60.50 (C-6), 45.64 (C-3'), 36.41 (CO*C*H_2), 34.36-22.67 (aliphatic C), and 17.36, 14.11 (*C*H_3) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.39-7.22 (m, 20H, aromatic H), 6.91 (d, 1H, J = 9.33 Hz, N*H*CO), 4.89, 4.63 (2d, 2H, J = 10.7 Hz, benzylic-H), 4.75, 4.69 (2d, 2H, J = 12.6 Hz, benzylic-H), 4.58, 4.49 (2d, 2H, J = 11.8 Hz, benzylic-H), 4.29 (d, 1H, J = 9.7 Hz, H-3), 3.87-3.49(m, 9H, H-1a, H-1b, H-1'a, H-1'b, H-2', H-4, H-5, H-6ax, H-6eq), 2.22-2.20 (m, 4H, COCH_2), 1.60-1.25 (m, 52H, aliphatic H), 1.11 (d, 3H, J = 6.9 Hz, CH_3-butyl), and 0.88 (2xt, 6H, 2xCH_3) ppm.

*2(**R**)-Hydroxy,3(**S**)-dodecanoylamidobutyl-β-**D**-fructopyranoside (28)*

A solution of **22** (199 mg, 0.245 mmol) in methanol (30 mL) was subjected to hydrogenolysis in the presence of palladium on charcoal (10%, 60 mg) at room temperature for 2 hr. The catalyst was removed by filtration, washed with methanol and the combined filtrate and washings concentrated *in vacuo* to give compound **28** as white crystals (91.9 mg, 83.2%). A sample of the product was crystallized (ether / ethanol) to give pure **28**. m.p. 131°C; $[\alpha]_D$ – 79.5° (MeOH); MS (FAB-Na^+) M/z 472 (M^++ Na^+), 288 (M^++ Na^+-$HCOC_{11}H_{23}$), 270 (M^++ Na^+-$HCOC_{11}H_{23}$, -H_2O). ^{13}C-NMR [$CDCl_3$ + CD_3OD, 75 MHz] δ 173.79 (*C*=O), 99.72 (C-2), 72.55 (C-3), 70.18 (C-4), 69.91 (C-5), 69.07 (C-2'), 63.68 (C-1), 62.69 (C-6), 62.53 (C-1'), 46.47 (C-3'), 36.50 (-COCH_2), 31.70-22.46 (aliphatic C) and 14.81, 13.84 (CH_3) ppm. ^{1}H-NMR [$CDCl_3$ + CD_3OD, 400 MHz] δ 4.06-4.01 (m, 1H, H-2'), 3.91(d, 1H, J = 9.7 Hz, H-3), 3.82, 3.80 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.2 Hz, H-4), 3.74-3.69 (m, 5H, H-1a', H-1a, H-5, H-6eq, H-6ax), 3.51-3.41 (m, 2H, H-1b, H-1b'), 2.17(t, 2H, J = 7.6 Hz, COCH_2), 1.58 (m, 2H, $CH_2CH_2CH_3$), 1.25 (m, 16H, aliphatic H), and 1.12 (d, 3H, J = 6.8 Hz, CH_3-butyl), 0.88 (t, 3H, CH_3) ppm. *Anal* calc for $C_{22}H_{43}O_8N$: C 58.77; H 9.64; N 3.12. Found: C 58.28; H 9.44; N 3.25%.

*2(**R**)-Hydroxy,3(**S**)-tetradecanoylamidobutyl-β-**D**-fructopyranoside (29)*

Compound **23** (200 mg, 0.238 mmol) was converted by the same procedure used to prepare compound **28**, to give **29** (88.6 mg, 78%) as white crystals. m.p. 129-130°C; $[\alpha]_D$ – 77.1° (MeOH); MS (FAB-Na^+) M/z 500.3 (M^++ Na^+), 317.3 (M^++ Na^+-$C_{13}H_{27}$), 299.3 (M^++ Na^+-$C_{13}H_{27}$ -H_2O). ^{13}C-NMR [$CDCl_3$ + CD_3OD, 75 MHz] δ 173.78 (*C*=O), 99.74 (C-2), 72.56 (C-3), 70.19 (C-4), 69.93 (C-5), 69.08 (C-2'), 63.69 (C-1), 62.70 (C-6), 62.54 (C-1'), 46.46 (C-3'), 36.52 (-COCH_2), 31.70-22.46 (aliphatic C) and 14.81, 13.84 (CH_3) ppm. ^{1}H-NMR [$CDCl_3$ + CD_3OD, 400 MHz] δ 4.05-4.01 (m, 1H, H-2'), 3.92(d, 1H, J = 9.7 Hz, H-3), 3.83, 3.81(dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.2 Hz, H-4), 3.73-3.70 (m, 5H, H-1a', H-1a, H-5, H-6eq, H-6ax), 3.50-3.39 (m, 2H, H-1b, H-1b'), 2.17 (t, 2H, J = 7.6 Hz, COCH_2), 1.59 (m, 2H, $CH_2CH_2CH_3$), 1.25 (m, 20H, aliphatic H), and 1.12 (d, 3H, J = 6.8 Hz, CH_3-butyl), 0.88 (t, 3H, CH_3) ppm. *Anal* calc for $C_{24}H_{47}O_8N$: C 60.35; H 9.92; N 2.93. Found: C 60.10; H 9.72, N 3.02%.

*2(**R**)-Hydroxy,3(**S**)-hexadecanoylamidobutyl-β-**D**-fructopyranoside (30)*

Compound **24** (238 mg, 0.275 mmol) was converted by the same procedure used to synthesize compound **28**, to give **30** (134.6 mg, 93%) as white crystals. m.p. 130-131°C; $[\alpha]_D$ –

74.5° (MeOH); MS (FAB-Na^+) M/z 528.4 (M^++ Na^+), 294.3 (M^++ Na^+-$C_{10}H_{18}O_6$). ^{13}C-NMR [$CDCl_3$ + CD_3OD, 75 MHz] δ 173.82 (*C*=O), 99.65 (C-2), 72.49 (C-3), 70.10 (C-4), 69.85 (C-5), 69.01 (C-2'), 63.63 (C-1), 62.63 (C-6), 62.45 (C-1'), 46.33 (C-3'), 36.34 (-CO*C*H_2), 31.65-22.40 (aliphatic C) and 14.76, 13.73 (*C*H_3) ppm. ^{1}H-NMR [$CDCl_3$ + CD_3OD, 400 MHz] δ 4.04-4.01 (m, 1H, H-2'), 3.90 (d, 1H, J = 9.7 Hz, H-3), 3.82, 3.80 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.2 Hz, H-4), 3.74-3.69 (m, 5H, H-1a', H-1a, H-5, H-6eq, H-6ax), 3.52-3.44 (m, 2H, H-1b, H-1b'), 2.17 (t, 2H, J = 7.6 Hz, CO*C*H_2), 1.60 (m, 2H, CH_2C*H*$_2CH_3$), 1.28 (m, 24H, aliphatic H), and 1.12 (d, 3H, J = 6.8 Hz, C*H*$_3$-butyl), 0.88 (t, 3H, C*H*$_3$) ppm. *Anal* calc for $C_{26}H_{51}O_8N$: C 61.75; H 10.17; N 2.77. Found: C 61.87; H 10.09; N 2.91%.

*2(**R**)-Dodecanoxy,3(**S**)-dodecanoylamidobutyl-β-**D**-fructopyranoside (31)*

A solution of **25** (156 mg, 0.157 mmol) in methanol (30 mL) containing palladium on charcoal (10%, 60 mg) was subjected to hydrogenolysis for 2 hr. The catalyst was removed by filtration, washed with methanol and the combined filtrate and washings concentrated *in vacuo* to give compound **31** (84.6 mg, 84.9%) as a colourless waxy material. $[\alpha]_D$ – 58.1° ($CHCl_3$); MS (FAB-Na^+) M/z 682, (M^++ Na^+) ^{13}C-NMR [$CDCl_3$ + CD_3OD, 75 MHz] δ 173.91, 173.76 (*C*=O), 99.73 (C-2), 72.58 (C-3), 70.16 (C-4), 69.93 (C-5), 69.12 (C-2'), 63.65 (C-1), 62.67 (C-6), 62.56 (C-1'), 46.46 (C-3'), 36.94 (CO*C*H_2), 34.33-22.65 (aliphatic C), and 14.84,14.08, 13.89 (CH_3) ppm. ^{1}H-NMR [$CDCl_3$ + CD_3OD, 400 MHz] δ 4.08-4.04 (m, 1H, H-2'), 3.91(d, 1H, J = 9.7 Hz, H-3), 3.82, 3.80 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.2 Hz, H-4), 3.74-3.66 (m, 5H, H-1a', H-1a, H-5, H-6eq, H-6ax), 3.51-3.43 (m, 2H, H-1b, H-1b'), 2.19(t, 2H, J = 7.6 Hz, CO*C*H_2), 1.60 (m, 2H, CH_2C*H*$_2CH_3$), 1.26 (m, 36H, aliphatic H), and 1.14 (d, 3H, J = 6.8 Hz, C*H*$_3$-butyl), 0.88 (2xt, 6H, 2xC*H*$_3$) ppm.

*2(**R**)-Tetradecanoxy,3(**S**)-tetradecanoylamidobutyl-β-**D**-fructopyranoside (32)*

Compound **26** (157.9 mg, 0.150 mmol) was converted by the same procedure used to prepare compound **31**, to give **32** (84 mg, 81%) as white crystals. A sample of the product was crystallized (isopropyl ether / n-pentane) to give pure **32**. m.p. 60°C; $[\alpha]_D$ – 57.9° ($CHCl_3$); MS (FAB-Na^+) M/z 710 (M^++ Na^+). ^{13}C-NMR [$CDCl_3$ + CD_3OD, 75 MHz] δ 173.89, 173.75 (*C*=O), 99.74 (C-2), 72.56 (C-3), 70.15 (C-4), 69.90 (C-5), 69.10 (C-2'), 63.66 (C-1), 62.69 (C-6), 62.55 (C-1'), 46.44 (C-3'), 36.94 (CO*C*H_2), 34.33-22.65 (aliphatic C), and 14.83,14.09, 13.92 (CH_3) ppm. ^{1}H-NMR [$CDCl_3$ + CD_3OD, 400 MHz] δ 4.07-4.02 (m, 1H, H-2'), 3.93(d, 1H, J = 9.7 Hz, H-3), 3.85, 3.83(dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.2 Hz, H-4), 3.73-3.69 (m, 5H, H-1a', H-1a, H-5, H-6eq, H-6ax), 3.50-3.40 (m, 2H, H-1b, H-1b'), 2.16 (t, 2H, J = 7.6 Hz, CO*C*H_2), 1.59 (m, 2H, CH_2C*H*$_2CH_3$), 1.25 (m, 44H, aliphatic H), and 1.13 (d, 3H, J = 6.8 Hz, C*H*$_3$-butyl), 0.88 (2xt, 6H, 2xC*H*$_3$) ppm. *Anal* calc for $C_{38}H_{72}O_9N$: C 66.44; H 10.56; N 2.04. Found: C 66.29; H 10.97; N 1.89%.

*2(**R**)-Hexadecanoxy,3(**S**)-hexadecanoylamidobutyl-β-**D**-fructopyranoside (33)*

Compound **27** was converted by the same procedure used to prepare compound **31** to give **33** (60 mg, 73.5%) as white crystals. m.p. 60°C; $[\alpha]_D$ – 57.3° ($CHCl_3$); MS (FAB-Na^+) M/z 766 (M^++ Na^+), 344 (M^++ Na^+-2x$C_{15}H_{31}$), 326 (M^++ Na^+-$C_{15}H_{31}$,-$C_{15}H_{31}$, -H2O). ^{13}C-NMR

[$CDCl_3$ + CD_3OD, 75 MHz] δ 173.86, 173.73 (*C*=O), 99.76 (C-2), 72.55 (C-3), 70.15 (C-4), 69.92 (C-5), 69.11 (C-2'), 63.65 (C-1), 62.68 (C-6), 62.53 (C-1'), 46.44 (C-3'), 36.94 ($COCH_2$), 34.33-22.65 (aliphatic C), and 14.85,14.07, 13.91 (CH_3) ppm. ^{1}H-NMR [$CDCl_3$ + CD_3OD, 400 MHz] δ 4.06-4.02 (m, 1H, H-2'), 3.92 (d, 1H, J = 9.7 Hz, H-3), 3.84, 3.82 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.2 Hz, H-4), 3.74-3.70 (m, 5H, H-1a', H-1a, H-5, H-6eq, H-6ax), 3.52-3.42 (m, 2H, H-1b, H-1b'), 2.17 (t, 2H, J = 7.6 Hz, $COCH_2$), 1.62 (m, 2H, $CH_2CH_2CH_3$), 1.26 (m, 52H, aliphatic H), and 1.14 (d, 3H, J = 6.8 Hz, CH_3-butyl), 0.88 (2xt, 3H, 2xCH_3) ppm. *Anal* calc for $C_{40}H_{76}O_9N$: C 67.19; H 10.71; N 1.96. Found: C 66.83; H 10.73; N 2.00%.

*2(**S**),3(**S**)-*N*-dodecanoylaziridinobutyl-1',3',4',5'-tetra-*O*-benzyl-β-**D**-fructopyranoside (34)*

A stirred cooled (–18°C) solution of **21** (258 mg, 0.42 mmol) in dichloromethane (10 mL) containing triethylamine (0.15 mL, 2.5 eq) was reacted with lauroyl chloride (0.1 mL, 0.466 mmol, 1.1 eq) and set aside for 1 hr. The reaction mixture was then diluted with dichloromethane (20 mL) and washed with 10% (w / w) citric acid (10 mL). The organic extract was dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (n-hexane-ethyl acetate, 1:1) of the crude material gave **34** (242 mg, 72.2%) as a pure colourless oil. $[\alpha]_D$ –35.0° ($CHCl_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 184.50 (*C*=O), 138.83, 138.62, 138.46, 137.93, 128.31, 128.26, 128.23, 128.17, 128.11, 128.08, 128.05, 127.76, 127.72, 127.69, 127.66, 127.63, 127.57, 127.47, 127.44, 127.32 (aromatic-C), 101.41 (C-2), 78.64 (C-3), 76.35 (C-4), 75.51 (benzylic-C), 73.54 (C-5), 72.14, 72.07, 70.25 (benzylic-C), 70.25 (C-1'), 63.21 (C-1), 61.04 (C-6), 37.53 (C-2'), 30.27 (C-3'), 31.87-22.65 (aliphatic C), and 18.21, 14.09 (CH_3) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.40-7.23 (m, 20H, aromatic H), 4.93, 4.60 (2d, 2H, J = 11.2 Hz, benzylic-H), 4.74, 4.65 (2d, 2H, J = 12.6 Hz, benzylic-H), 4.64, 4.42 (2d, 2H, J = 11.9 Hz, benzylic-H), 4.34 (d, 1H, J = 10.1 Hz, H-3), 4.00 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.19 Hz, H-4), 3.83 (dd, 1H, $J_{5,6eq}$ = 1.89 Hz, $J_{6ax,6eq}$ = -12.3 Hz, H-6eq), 3.80 (dd, 1H, $J_{5,6ax}$ = 1.87 Hz, $J_{6ax,6eq}$ = -12.3 Hz, H-6ax), 3.79 (m, 1H, H-5), 3.74 (2d, 1H, J = -10.1 Hz, H-1a), 3.60 (2d, 1H, J = -10.1 Hz, H-1b), 3.64 (dd, 1H, J = 6.37 Hz, H-1'a), 3.39 (dd, 1H, J = 6.37 Hz, H-1'b), 1.90 (m, 1H, H-2'), 1.74 (m, 1H, H-3'), 1.19 (d, 3H, $J_{3',4'}$ = 5.5 Hz, CH_3) ppm.

*2(**S**),3(**S**)-*N*-tetradecanoylaziridinobutyl-1,'3,'4,'5'-tetra-*O*-benzyl-β-**D**-fructopyranoside (35)*

Compound **35** was synthesized by treatment of **21** (282 mg, 0.463 mmol) with myristoyl chloride (0.13 mL, 0.509 mmol, 1.1 eq), using the same procedure as described for the synthesis of **34**. Column chromatography (n-hexane-ethyl acetate, 1:1) of the crude material gave **35** (265 mg, 69.9%) as a pure colourless oil. $[\alpha]_D$ –34.0° ($CHCl_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 183.50 (*C*=O), 138.86, 138.59, 138.48, 137.93, 128.25, 128.08, 128.04, 127.76, 127.69, 127.58, 127.48, 127.43, 127.30 (aromatic-C), 101.65 (C-2), 78.65 (C-3), 76.19 (C-4), 75.42 (benzylic-C), 73.67 (C-5), 73.56, 72.19, 71.24 (benzylic-C), 70.27 (C-1'), 61.27 (C-1), 61.18 (C-6), 42.16 (C-2'), 37.30 (C-3'), 36.85 ($COCH_2$), 31.89-22.66 (aliphatic C), and 16.21, 14.09 (CH_3) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.40-7.22 (m, 20H, aromatic H), 4.92, (d, 1H, J = 11.2 Hz, benzylic-H), 4.74, 4.65 (2d, 2H, J = 12.6 Hz, benzylic-H), 4.65-4.59 (m, 4H, benzylic-H), 4.43, (d, 1H, J = 11.9 Hz, benzylic-H), 4.32 (d, 1H, J = 10.0 Hz, H-3), 4.00 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.1 Hz, H-4), 3.86 (dd, 1H, $J_{5,6eq}$ = 1.7 Hz, $J_{6ax,6eq}$ = -12.3 Hz, H-6eq), 3.78 (m, 1H, H-5), 3.73 (d,

1H, J = -10.2 Hz, H-1a), 3.66 (dd, 1H, J = 3.96 Hz, H-1'a), 3.62-3.55 (m, 3H, H-1'b, H-1b, H-6ax), 2.43 (t, 2H, COCH_2), 2.28-2.0 (m, 2H, H-2', H-3'), 1.56 (m, 2H, CH_2CH$_3$), 1.26 (m, 17H, aliphatic H), 0.87 (t, 3H, 6.7 Hz, CH_3) ppm.

*2(**R**),3(**S**)-N-hexadecanoylaziridinobutyl-1',3',4',5'-tetra-O-benzyl-β-**D**-fructopyranoside (**36**)*

Compound **36** was synthesized by treatment of **21** (178 mg, 0.292 mmol) with palmitoyl chloride (0.13 mL, 0.321 mmol, 1.1 eq), using the same procedure as described for the synthesis of **34**. Column chromatography (n-hexane-ethyl acetate, 1:1) of the crude material gave **36** (216 mg, 87.2%) as a colourless oil. $[\alpha]_D$ –33.4° ($CHCl_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 183.52 (*C*=O), 138.88, 138.61, 138.49, 137.95, 128.26, 128.09, 128.06, 127.77, 127.70, 127.60, 127.49, 127.44, 127.31, 126.91 (aromatic-C), 101.66 (C-2), 78.66 (C-3), 76.21 (C-4), 75.43 (benzylic-C), 73.69 (C-5), 73.57, 72.20, 71.26 (benzylic-C), 70.28 (C-1'), 61.29 (C-1), 61.19 (C-6), 42.17 (C-2'), 37.31 (C-3'), 36.86 (CO*C*H$_2$), 31.90-22.67 (aliphatic C), and 16.22, 14.10 (*C*H$_3$) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.41-7.24 (m, 20H, aromatic H), 4.92, (d, 1H, J = 11.2 Hz, benzylic-H), 4.74, 4.69 (2d, 2H, J = 12.8 Hz, benzylic-H), 4.66-4.62(m, 4H, benzylic-H), 4.44 (d, 1H, J = 11.9 Hz, benzylic-H), 4.33 (d, 1H, J = 10.1 Hz, H-3), 4.00 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.12 Hz, H-4), 3.86 (dd, 1H, $J_{5,6eq}$ = 1.7 Hz, $J_{6ax,6eq}$ = -12.3 Hz, H-6eq), 3.79 (m, 1H, H-5), 3.74 (d, 1H, J = -10.2 Hz, H-1a), 3.66 (dd, 1H, J = 3.96 Hz, H-1'a), 3.62-3.57 (m, 3H, H-1'b, H-1b, H-6ax), 2.44 (t, 2H, COCH_2), 2.29-2.24 (m, 2H, H-2', H-3'), 1.54 (m, 2H, CH_2CH$_3$), 1.26 (m, 24H, aliphatic H), 0.87 (t, 3H, J = 6.7 Hz, CH_3) ppm.

*3(**R**)-Dibenzyl,2(**S**)-dodecanoylamidobutyl-1',3',4',5'-tetra-O-benzyl-β-**D**-fructopyranoside-3-phosphate (**37**)*

A stirred solution of **34** (186 mg, 0.235 mmol) in dichloromethane (5 mL) was treated with dibenzyl hydrogen phosphate (71.9 mg, 0.258 mmol, 1.1 eq) for 1 hr. The reaction mixture was diluted with dichloromethane (20 mL) and washed with saturated aqueous sodium hydrogencarbonate (20 mL). The organic extract was dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (n-heptane-ethyl acetate, 2:1) of crude material gave **37** (181.6 mg, 72.2%) as a pure colourless oil. $[\alpha]_D$ –25.1° ($CHCl_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 172.84 (*C*=O), 139.28, 138.57, 137.85, 135.68, 135.41, 129.69, 128.59, 128.27, 128.18, 128.05, 128.82, 127.66, 127.54, 127.49, 127.39, 127.19 (aromatic-C), 101.15 (C-2), 78.53 (C-3), 76.66 (C-4), 75.73, 73.64 (benzylic-C), 73.39 (C-5), 71.67, 71.13, 70.35 (benzylic-C), 69.50 (benzylic-C), 69.28 (C-1'), 61.25 (C-1), 58.98 (C-6), 52.71 (C-2'), 52.39 (C-3'), 36.37 (CO*C*H$_2$), 31.88-22.65 (aliphatic C), and 18.91, 14.08 (*C*H$_3$) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.39-7.20 (m, 30H, aromatic H), 6.46 (d, 1H, N*H*CO), 5.05-4.92 (m, 5H, benzylic-H), 4.71, 4.66 (2d, 2H, J = 12.6 Hz, benzylic-H), 4.64, 4.40 (2d, 2H, J = 11.7 Hz, benzylic-H), 4.28 (d, 1H, J = 10.0 Hz, H-3), 4.06 (ddd, 1H, 2'), 3.96 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.0 Hz, 4), 3.74 (dd, 1H, $J_{5,6eq}$ = 2.0 Hz, $J_{6ax,6eq}$ = -12.5 Hz, H-6eq), 3.72 (dd, 1H, $J_{5,6ax}$ = 1.6 Hz, $J_{6ax,6eq}$ = -12.5 Hz, H-6ax), 3.69 (m, 1H, H-5), 3.68 (d, 1H, J = -10.1 Hz, H-1a), 3.66 (dd, 1H, $J_{1'a,1'b}$ = 2.3 Hz, H-1'a), 3.63 (dd, 1H, $J_{1'a,1'b}$ = 2.3 Hz, H-1'b), 3.58 (d, 1H, J = -10.1 Hz, H-1b), 3.43 (dd, 1H, H-3'), 1.84-1.80 (m, 2H, COCH_2), 1.44 (m, 2H, CH_2CH$_3$), 1.32-1.25 (m, 24H, aliphatic H), 0.88 (t, 3H, CH_3) ppm.

*3(**R**)-Dibenzyl,2(**S**)-tetradecanoylamidobutyl-1',3',4',5'-tetra-*O*-benzyl-β-**D**-fructopyranoside-3-phosphate (38)*

Compound **38** (189 mg) was obtained by the same procedure used to synthesize compound **37**. Column chromatography (n-heptane-ethyl acetate, 2:1) of crude material gave **38** (189 mg, 69.9%) as a colourless oil. $[\alpha]_D$ –25.7° ($CHCl_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 172.96 (*C*=O), 139.05, 138.56, 137.83, 135.58, 128.74, 128.69, 128.62, 128.54, 128.41, 128.35, 128.30, 128.26, 128.22, 128.10, 128.04, 127.97, 127.93, 127.85, 127.82, 127.72, 127.65, 127.59, 127.43, 127.41, 127.33 (aromatic-C), 101.15 (C-2), 78.48 (C-3), 76.64 (C-4), 75.83, 73.65 (benzylic-C), 73.65 (C-5), 71.66, 71.15, 70.29, 69.42 (benzylic-C), 69.36 (C-1'), 61.26 (C-1), 59.10 (C-6), 52.54 (C-2'), 52.46 (C-3'), 36.36 (CO*C*H_2), 31.90-22.67 (aliphatic C), and 18.92, 14.11 (*C*H_3) ppm. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.38-7.20 (m, 30H, aromatic H), 6.54 (d, 1H, N*H*CO), 5.02-4.92 (m, 5H, benzylic-H), 4.70, 4.65 (2d, 2H, J = 12.6 Hz, benzylic-H), 4.64, 4.42 (2d, 2H, J = 11.8 Hz, benzylic-H), 4.29 (d, 1H, J = 10.0 Hz, H-3), 4.06 (ddd, 1H, H-2'), 3.94 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.0 Hz, H-4), 3.73 (dd, 1H, $J_{5,6eq}$ = 2.0 Hz, $J_{6ax,6eq}$ = -12.5 Hz, H-6eq), 3.70 (dd, 1H, $J_{5,6ax}$ = 1.6 Hz, $J_{6ax,6eq}$ = -12.5 Hz, H-6ax), 3.69 (m, 1H, H-5), 3.68 (d, 1H, J = -10.1 Hz, H-1a), 3.66 (dd, 1H, $J_{1'a,1'b}$ = 2.3 Hz, H-1'a), 3.64 (dd, 1H, $J_{1'a,1'b}$ = 2.3 Hz, H-1'b), 3.60 (d, 1H, J = -10.1 Hz, H-1b), 3.43 (dd, 1H, H-3'), 1.88-1.82 (m, 2H, COCH_2), 1.45 (m, 2H, CH_2CH$_3$), 1.33-1.25 (m, 20H, aliphatic H), 0.88 (t, 3H, CH_3) ppm.

*3(**R**)-Dibenzyl,2(**S**)-hexadecanoylamidobutyl-1',3',4',5'-tetra-*O*-benzyl-β-**D**-fructopyranoside-3-phosphate (39)*

Compound **36** (353.6 mg, 0.417 mmol) was converted by the same procedure used to synthesize compound **37**. Column chromatography (n-heptane-ethyl acetate, 2:1) of the crude material gave **39** (352 mg, 75%) as a pure colourless oil. $[\alpha]_D$ – 25.9° ($CHCl_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 172.85 (*C*=O), 139.14, 138.53, 137.80, 128.57, 128.49, 128.26, 128.22, 128.18, 128.05, 127.88, 127.81, 127.78, 127.68, 127.62, 127.56, 127.39, 127.36, 127.23 (aromatic-C), 101.12 (C-2), 78.47 (C-3), 76.62 (C-4), 75.88, 73.62 (benzylic-C), 73.33 (C-5), 71.63, 71.10, 70.29, 69.40 (benzylic-C), 69.36 (C-1'), 61.22 (C-1), 59.02 (C-6), 52.55 (C-2'), 52.44 (C-3'), 36.34 (CO*C*H_2), 31.88-22.64 (aliphatic C), and 18.92, 14.08 (*C*H_3) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.39-7.23 (m, 30H, aromatic H), 6.54 (d, 1H, N*H*CO), 5.05-4.92 (m, 5H, benzylic-H), 4.71, 4.66 (2d, 2H, J = 12.6 Hz, benzylic-H), 4.64, 4.42 (2d, 2H, J = 11.8 Hz, benzylic-H), 4.29 (d, 1H, J = 10.0 Hz, H-3), 4.06 (ddd, 1H, H-2'), 3.95 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.0 Hz, H-4), 3.73 (dd, 1H, $J_{5,6eq}$ = 2.0 Hz, $J_{6ax,6eq}$ =-12.5 Hz, H-6eq), 3.71 (dd, 1H, $J_{5,6ax}$ = 1.6 Hz, $J_{6ax,6eq}$ = -12.5 Hz, H-6ax), 3.69 (m, 1H, H-5), 3.68 (d, 1H, J = -10.1 Hz, H-1a), 3.66 (dd, 1H, $J_{1'a,1'b}$ = 2.3 Hz, H-1'a), 3.63 (dd, 1H, $J_{1'a,1'b}$ = 2.3Hz, H-1'b), 3.58 (d, 1H, J = -10.1 Hz, H-1b), 3.43 (dd, 1H, H-3'), 1.87-1.81 (m, 2H, COCH_2), 1.45 (m, 2H, CH_2CH$_3$), 1.33-1.25 (m, 24H, aliphatic H), 0.88 (t, 3H, CH_3) ppm.

*3(**R**)-Disodium,2(**S**)-dodecanoylamidobutyl-β-**D**-fructopyranoside-3-phosphate (40)*

A solution of **37** (121 mg, 0.113 mmol) in methanol (30 mL) containing palladium on charcoal (10%, 60 mg) was hydrogenolyzed at room temperature for 2 hr. The catalyst was removed by filtration, washed with methanol and the combined filtrate and washings

concentrated *in vacuo* to reduce the volume of methanol, and water (10 mL) were added. The mixture was then passed through an ion-exchange column (Dowex 50Wx2, sodium form). The methanol remaining in the eluate was removed *in vacuo,* and the resultant mixture was lyophilized to give **40** (46 mg, 70.8%) as white crystals. m.p. 195°C; $[\alpha]_D$ – 48.7° (MeOH); MS (FAB-Na^+) M/z 390 (M^++ Na^+ -$COC_{11}H_{23}$). ^{13}C-NMR (D_2O, 75 MHz) δ 178.16 (*C*=O), 101.71 (C-2), 72.08 (C-3), 70.82 (C-4), 70.41 (C-5), 69.82 (C-2'), 65.13 (C-1), 62.65 (C-6), 62.05 (C-1'), 55.66 (C-3'), 37.34 (-CO*C*H_2), 32.54-23.37 (aliphatic C) and 19.70, 14.73 (*C*H_3) ppm. ^{1}H-NMR (D_2O, 400 MHz) δ 6.2 (d, 1H, N*H*CO), 4.14 (m, 1H, H-2'), 3.97-3.65 (m, 8H, H-1a', H-1, H-3, H-4, H-5, H-6), 3.52-3.50 (m, 3H, H-1b', H-3'), 2.21 (t, 2H, COCH_2), 1.53 (m, 2H, $CH_2CH_2CH_3$), 1.25 (m, 19H, aliphatic H), and 0.80 (t, 3H, CH_3) ppm. *Anal* calc for $C_{22}H_{42}NNa_2O_{11}P$: C 46.07; H 7.38; N 2.44. Found: C 45.90; H 7.32; N 2.25%.

*3(**S**)-Disodium,2(**S**)-tetradecanoylamidobutyl-β-**D**-fructopyranoside-3-phosphate (**41**)*

Compound **41** (50 mg) was obtained by the same procedure used to synthesize compound **40** from **37**, to give **41** (50mg, 72.4%) as white crystals. m.p. 205°C; $[\alpha]_D$ – 45.1° (MeOH); MS (FAB-Na^+) M/z 738 (M^++ Na^+). ^{13}C-NMR (D_2O, 75 MHz) δ 177.17 (*C*=O), 101.76 (C-2), 72.05 (C-3), 70.81 (C-4), 70.45 (C-5), 69.67 (C-2'), 65.18 (C-1), 62.62 (C-6), 62.11 (C-1'), 55.45 (C-3'), 37.38 (-CO*C*H_2), 32.34-23.78 (aliphatic C) and 19.68, 14.56 (*C*H_3) ppm. ^{1}H-NMR (D_2O, 400 MHz) δ 6.2 (d, 1H, N*H*CO), 4.12 (m, 1H, H-2'), 3.95-3.63 (m, 8H, H-1a', H-1, H-3, H-4, H-5, H-6), 3.53-3.50 (m, 3H, H-1b', H-3'), 2.21 (t, 2H, COCH_2), 1.52 (m, 2H, $CH_2CH_2CH_3$), 1.25 (m, 23H, aliphatic H), and 0.82 (t, 3H, CH_3) ppm. *Anal* calc for $C_{24}H_{46}NNa_2O_{11}P$: C 47.92; H 7.71; N 2.33. Found: C 47.61; H 7.81; N 2.11%.

*3(**R**)-Disodium,2(**S**)-hexadecanoylamidobutyl- β-**D**-fructopyranoside-3-phosphate (**42**)*

Compound **42** (103 mg, 69.2%) was prepared by the same procedure used to synthesize compound **40** from **37**. m.p. 198°C; $[\alpha]_D$ – 44.4° (MeOH); MS (FAB-Na^+) M/z 766 (M^++ Na^+). ^{13}C-NMR (D_2O, 75 MHz) δ 176.84 (*C*=O), 101.79 (C-2), 71.90 (C-3), 70.80 (C-4), 70.58 (C-5), 69.77 (C-2'), 65.27 (C-1), 62.55 (C-6), 62.22 (C-1'), 55.42 (C-3'), 37.42 (-CO*C*H2), 33.18-23.88 (aliphatic C) and 19.64, 15.15 (*C*H_3) ppm. ^{1}H-NMR (D_2O, 400 MHz) δ 6.2 (d, 1H, N*H*CO), 4.19 (m, 1H, H-2'), 3.92-3.57 (m, 8H, H-1a', H-1, H-3, H-4, H-5, H-6), 3.52-3.50 (m, 3H, H-1b', H-3'), 2.19 (t, 2H, COCH_2), 1.54 (m, 2H, $CH_2CH_2CH_3$), 1.23 (m, 27H, aliphatic H), and 0.83 (t, 3H, CH_3) ppm. *Anal* calc for $C_{26}H_{50}NNa_2O_{11}P$: C 49.60; H 8.00; N 2.22. Found: C 49.36; H 8.18; N 2.08%.

6.5 References

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CHAPTER 7

SYNTHESIS OF SOME ACYLAMINO-PHOSPHATES FROM 2,3-DIHYDROXYALKYL β-D-FRUCTOPYRANOSIDE DERIVATIVES

7.1 Introduction

During a recent study [1a,b] at the university of Nijmegen the effects of molecular chirality on surfactant behaviour, especially at a supramolecular level were investigated. There is a dearth of information on how supramolecular chirality relates to molecular organisation in aggregates, or guidelines for predicting chiral aggregate formation due mainly to a lack of suitable intemediates. The aforementioned study, *inter alia* optically active surfactant molecules based on a phospholipid type-skeleton containing a long chain amide function for the construction of chiral aggregates. These types of structures require a high degree of organisation within the aggregate so as to enable them to transfer the molecular chirality to the supramolecular level. A series of chiral molecules based on a phospholipid skeleton and having an amide linked long-chain hydrocarbon group at C-2 were prepared (Figure 7.1).

Phospholipid molecules can form tubular, rod-like or helical structures.[2] It has been shown that chiral synthetic surfactants can also form similar superstructures. A high degree of organization with the aggregate is required to transfer molecular chirality to the supramolecular level. This can be achieved by hydrogen bonding or π-π stacking. Hydrogen bonded chains of secondary amides have been used with good effect.

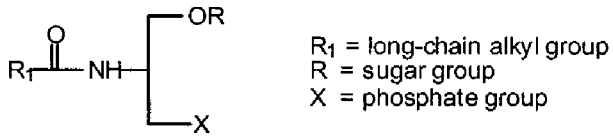


Figure 7.1

Carbohydrates are stereochemically pure compounds and can be used as synthetic chiral building blocks in the synthesis of chiral amphiphiles. Incorporation of a sugar moiety as the polar head group in these types of surfactant molecules could enhance the degree of organisation within the aggregates. It was considered worthwhile to synthesize alternative chiral surfactant molecules based on a phospholipid type skeleton and with a sugar head group containing a long-chain amidic function derived from the dihydroxylated glycosides of D-fructose for eventual investigations into the effects of increased chirality (sugar ring + chiral aglycon) on aggregate formation.

Surfactants are "surface active agents" which can be adsorbed at interfaces and change the properties of these interfaces.[2] Surfactants possess a dualistic character, that is, they have a hydrophilic head group which is water soluble, and a hydrophobic part that tends to minimize

water contact. The head group can be anionic (e.g. sulfates, sulfonate, phosphate, carboxylate), cationic (e.g. ammonium, alkyl substituted ammonium, pyridinium), zwitterionic (e.g. betain), or non-ionic (poly glycol ether, or carbohydrates).[3] The hydrophobic group usually consist of one or more alkyl chains which can be linear, branched or unsaturated. It is the hydrophilic-hydrophobic-balance of these groups within the individual molecules that provide the characteristic surfactant properties such as wetting, foaming, emulsification, dispersion, and solubilization. Surfactants have numerous uses, including the manufacturing of cleaning agents in laundries, dish washing, cosmetics and pharmaceuticals, paints and plastics, in the manufacturing of textiles and fibres, in the food industry, pesticides, and in oil production processes.

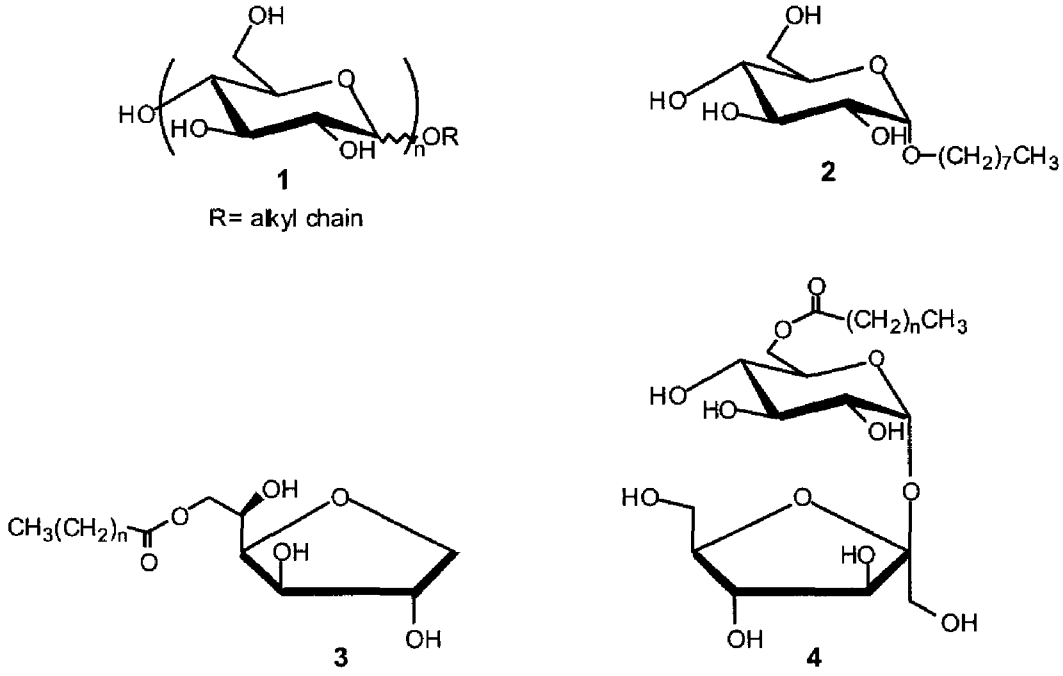


Figure 7.2: Some representative commercially produced carbohydrate-based surfactants: alkyl polyglucoside **1**, octyl α-D-glucopyranoside **2**, sorbitan fatty acid ester **3**, and sucrose fatty acid ester **4**.

Most of the surfactants produced commercially are based on petrochemicals. In the long term, fossils feedstock will become exhausted and products based on annually renewable materials will become more important. Carbohydrates can provide an excellent source of raw-materials for producing a broad range of surfactants. Carbohydrate-based surfactants consist of a carbohydrate moiety as the hydrophilic head group linked to a hydrophobic part, i.e fatty acid or alcohol, usually by ether, ester, or amide bonds. Unique properties, such as non-toxicity, skin compatibility, environmentally benign, and biodegradability, suggest a wide range of application for these surfactants. The starting material for the majority of sugar-based derivatives has been glucose, which can be obtained from sucrose (cane or beet sugar), potatoes, or wheat.

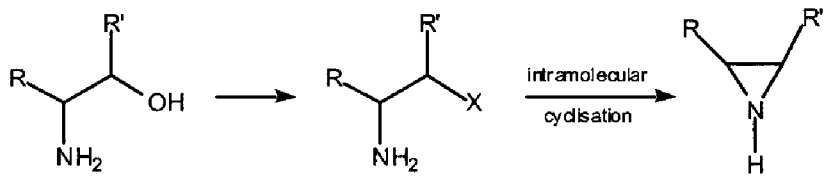
There is also increasing interest in the synthesis of new products based on D-fructose,[4] e.g. non-ionic surfactants. This is due to the fact that D-fructose is now becoming more easily available in increased amounts, e.g. *via* high fructose syrup. The production of high fructose corn syrup from starch on a commercial basis has been carried out since 1968 [5] *via* a two step enzyme-mediated process. The enzyme catalyzed hydrolysis of inulin is a more recent alternative source of high fructose syrup, and pure D-fructose.[4,5]

This chapter reports on the synthesis of some carbohydrate-based surfactants of the acylamino-phosphate type (*vide infra*) starting from some derivatives of D-fructose.

7.2 Results and discussion

7.2.1 Synthesis of aziridine and *N*-acyl aziridine derivatives from D-fructose

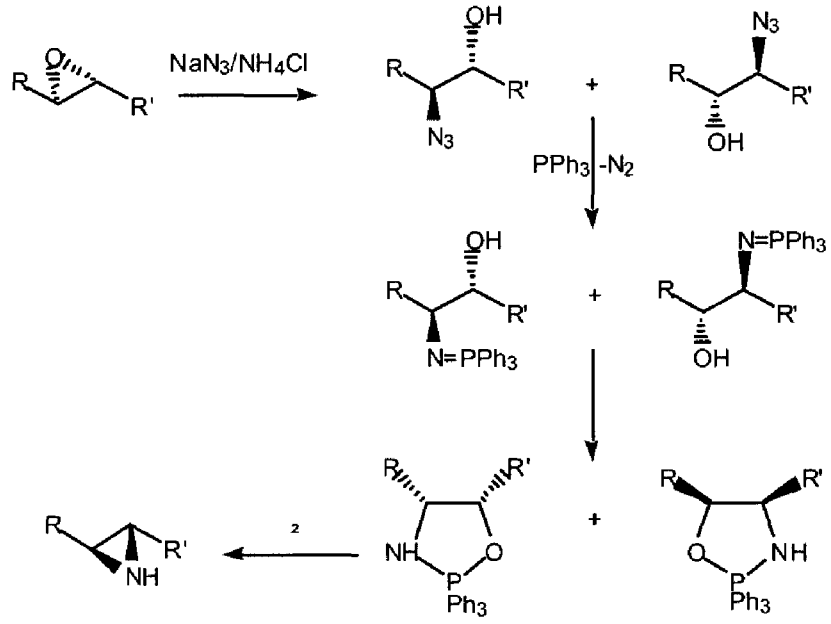
The ability of aziridines to undergo highly regio- and stereoselective ring opening renders them of great value in organic synthesis.[5,6] They have also been observed in nature, where a number of molecules possessing an aziridine ring have been shown to exhibit potent biological activity.[7-9a-c] In general, aziridines are synthesized using 1,2 amino alcohols as precursors.[10,11] In these cases the hydroxyl functional group is converted to a good leaving group, e.g. a sulfonate ester, which on intramolecular nucleophilic displacement yields the aziridine. By using enantiopure amino alcohols, the synthesis of asymmetric aziridines is possible.



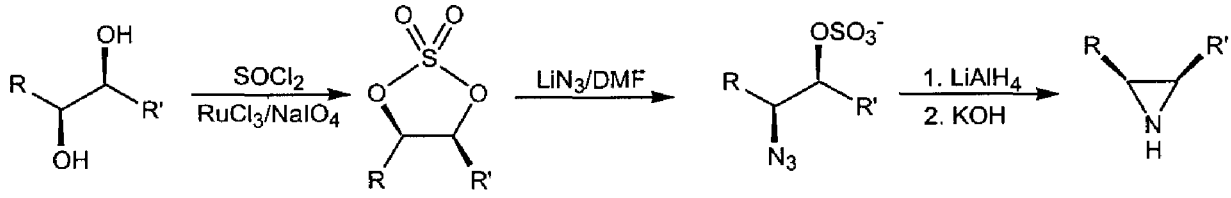
Scheme 7.1: General synthesis of aziridines from amino alcohols

The regiospecific ring opening of oxiranes by azide ions to give azido alcohols can be exploited for the synthesis of aziridines.[12a-c,13] Reduction of the azide moiety of the vicinal azido alcohol, for instance, with triphenylphosphine in a Staudinger-type reaction,[12a-c,13,14] yields initially an imino phosphirane and then an oxazaphosphine intermediate, this is normally not isolated prior to the thermally-induced cyclization to yield the aziridine. This procedure has been also used in the preparation of carbohydrate-derived aziridines.[15a-c,16]

An alternative route to the synthesis of aziridines would be *via* cyclic sulfates obtained from vicinal diols.[17,18] The pathway for this conversion of a diol *via* a cyclic sulfate intermediate involves two consecutive nucleophilic displacement reactions with the final displacement being an intramolecular reductive animation process (scheme 7.3).



Scheme 7.2: Synthesis of aziridines [12a-c]



Scheme 7.3: Synthesis of aziridine via cyclic sulfates

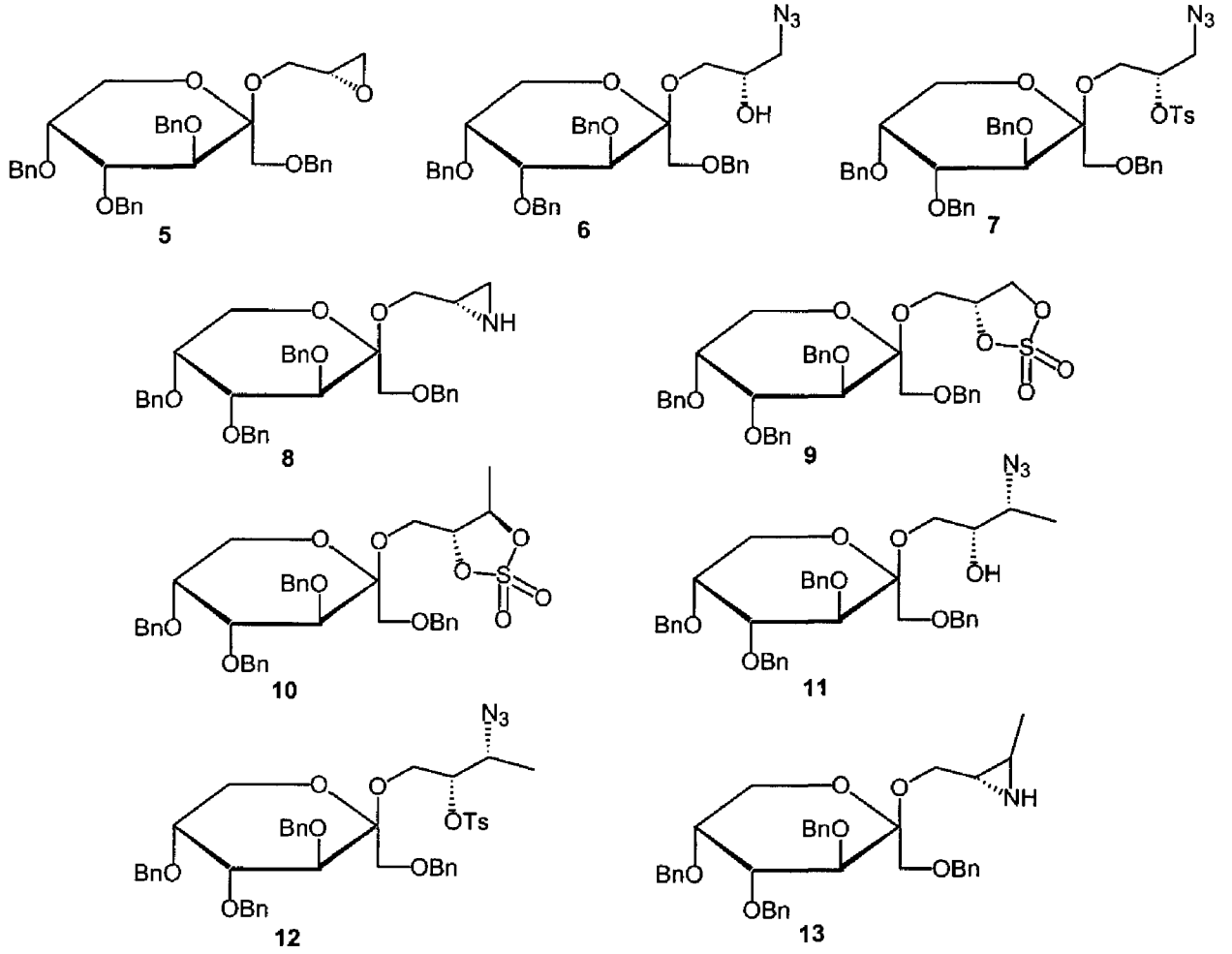
It was decided to investigate the synthesis of aziridine derivatives derived from the oxirane **5** and from the cyclic sulfates **9** and **10**, which have been described in chapter 5 and 6. It was planned to use the two routes outlined above, both of which involved the formation of azido alcohols as interim products.

The azido alcohol **6** was obtained as a single product on treatment of the oxirane **5** in aqueous 2-methoxyethanol with sodium azide in the presence of ammonium sulfate (see Chapter 5). The second route for the synthesis of aziridine derivatives involved formation of azido alcohols **6** and **11** from the cyclic sulfates **9** and **10** obtained from the corresponding diols (see Chapter 5 and 6 for details). Lithium azide was used in the ring opening reaction of compounds **9** and **10** since it has a much greater solubility in *N,N*-dimethylformamide (~1g / 10 mL) compared with the corresponding sodium salt.[19]

Reaction of compound **6** with *p*-toluenesulfonyl chloride-pyridine in the usual manner yielded the corresponding sulfonate ester **7** (92%). Reduction ($LiAlH_4$) of **7** in ether occurred with concomitant cyclization to give the aziridine **8** in 68% overall yield from the azido alcohol **6**, after purification by column chromatography.

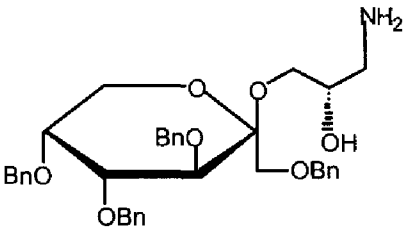
In a similar sequence of reactions, the azido alcohol **11** yielded the corresponding sulfonate ester **12** (70%) which was reduced ($LiAlH_4$) to the aziridine **13** in 69% overall yield. In this case the reduction of the sulfonate ester **12** using lithium aluminium hydride in dry ether

did not proceed as expected even after long reaction periods (24-48 hr). Compound **13** was successfully obtained when the reduction was performed in dry tetrahydrofuran at 25°C. The reason for this observed solvent-related difference in reactivity is not clear. It is known that the course of reductions with lithium aluminium hydride can be affected by the choice of solvent, but the effect has not been examined systematically. Both compound **8** and **13** needed to be purified by column chromatography (CH_2Cl_2-MeOH, 9:1) but could be isolated satisfactorily. The formation of enantiomerically pure aziridines from some allyl β-**D**-glucopyranosides has been reported.[20] Attempted purification of these derivatives by column chromatography produced only decomposition products.



Initially, it was thought that Staudinger-type reductions of the azide groups of **6** and **11** would yield the desired aziridines directly. This was based on literature precedents in which both cyclic and acyclic [14] vicinal azido alcohols have been shown to give aziridines directly when treated with triphenyl phosphine. However, when compounds **6** and **11** were treated with triphenylphosphine in different solvents (toluene, ether, tetrahydrofuran or acetonitrile), only the corresponding amino alcohols **14** and **15** were obtained, after work-up. Similar results were reported [21] during the synthesis of aziridine-2-lactones from **D**-ribose and **D**-lyxose. When methyl-3-azido-3-deoxy-methyl β-**D**-xylofuranoside (**16**) was reacted with triphenylphosphine in tetrahydrofuran, only the 3-deoxy-3-amino-**D**-xylofuranoside (**17**) could be isolated. It was

suggested that the *trans* arrangement of the 2,3 substituents prevents the hydroxyl group from reacting intramolecularly with the phosphonimine formed at C-3. These results contrast non-carbohydrate systems in which a *trans* azido alcohol was shown to give an aziridine under the same conditions.[22,23] When the reaction was performed in *N,N*-dimethylformamide, only trace amounts of aziridine **8** (less than 10%) were formed, together with the corresponding amino alcohol. Low yields of the desired product could be due to hydrolysis of the phosphinimine intermediate during the reaction, resulting in the formation of the amino alcohol, which was isolated as the major product.



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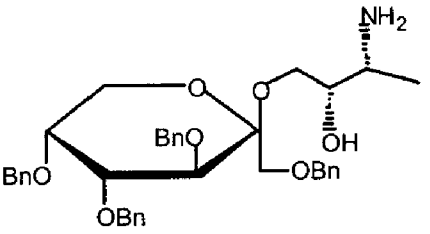

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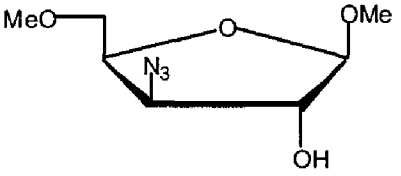

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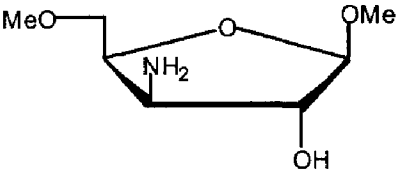

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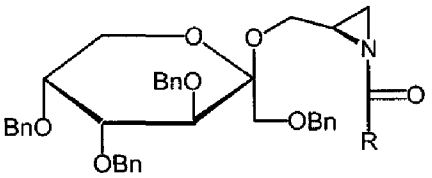
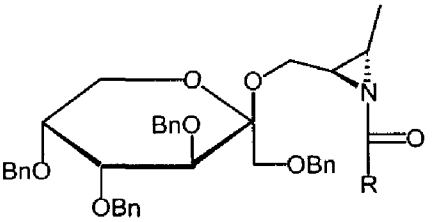
The aziridine **8** was also observed to be rather unstable and it decomposed when stored above 0°C or remained in solution for short periods (i.e. two days in $CHCl_3$). Immediate reaction of the aziridine with acyl chlorides was considered advisable (*vide infra*). Compound **13** was, however, considerably more stable and no decomposition products were detected after two days at 25°C.

The aziridines **8** and **13** were subsequently acylated using different (C_{12}, C_{14}, C_{16}) fatty acid chlorides in dichloromethane solution, in the presence of triethylamine acting as a base. The crude products obtained, after the usual work-up procedures, were purified by column chromatography (n-hexane-ethyl acetate, 3:1) to give the *N*-acylated aziridines **18-20** and **21-23**, respectively, in reasonable yields. All of the products were non-crystalline.



18 R = $C_{11}H_{23}$ (77%)
19 R = $C_{13}H_{27}$ (62%)
20 R = $C_{15}H_{31}$ (72%)

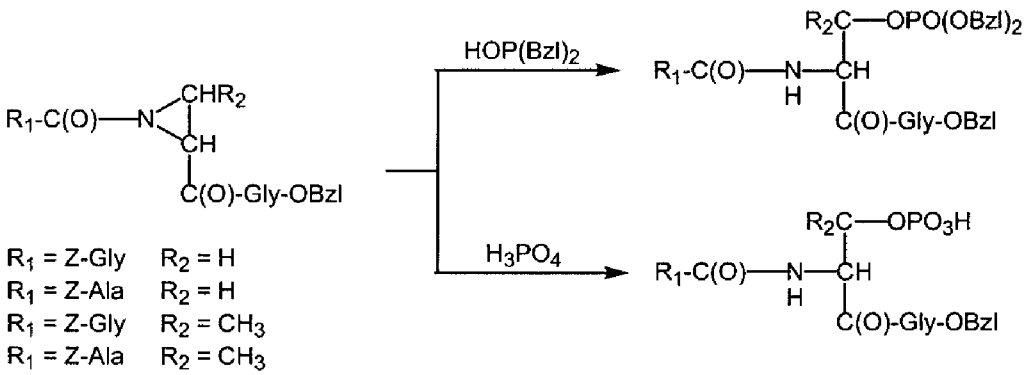


21 R = $C_{11}H_{23}$ (72%)
22 R = $C_{13}H_{27}$ (70%)
23 R = $C_{15}H_{31}$ (87%)

7.2.2 Ring opening of *N*-acyl aziridines with dibenzyl hydrogen phosphate

N-Acyl aziridine derivatives have been employed in the synthesis of some unusual amide containing surfactants based on a phospholipid skeleton.[1a,b] It should be possible to obtain new forms of amide-containing surfactants derived from compounds **18-23** (*vide supra*) containing *N*-acyl aziridine functions derived from fructosyl derivatives. This will lead to a series of new chiral surfactant molecules possessing both a phospholipid type skeleton and monosaccharide moiety.

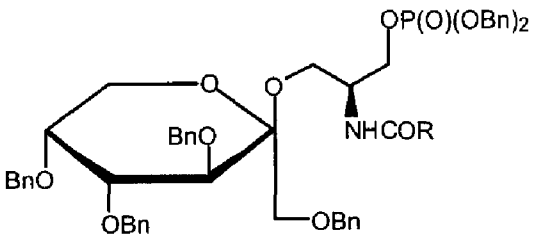
Ring opening of certain acylated aziridine peptides using either dibenzyl hydrogen phosphate or phosphoric acid for the synthesis of phosphopeptide derivatives has been reported [24] (Scheme 7.4). The use of aziridines as starting materials in these syntheses enabled the introduction of both amide and phosphate groups to be achieved in successive steps. The introduction of an amide group by acylation of the aziridine function was not only important for peptide coupling reactions, but also as an activation step for the incorporation of a phosphate group by opening of the aziridine ring.[24] Starting from a suitable aziridine derivative, only two reaction steps were required for the introduction of an amidic function and a phosphate group through opening of an appropriate acylated aziridine ring.[1b]



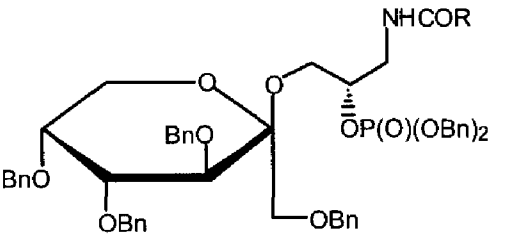
R_1 = Z-Gly R_2 = H
R_1 = Z-Ala R_2 = H
R_1 = Z-Gly R_2 = CH_3
R_1 = Z-Ala R_2 = CH_3

Scheme 7.4: Synthesis of phosphopeptides via aziridine

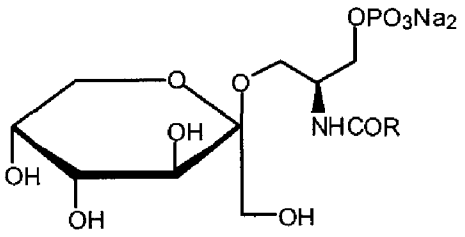
The preparation of novel surfactants derived from the fructose derivatives **8** and **13** involved the same type of ring-opening reaction using the activated *N*-acyl aziridines **18-23** with dibenzyl hydrogen phosphate as the reagent. When a solution of **18** in dichloromethane was treated with dibenzyl hydrogen phosphate at room temperature for 3 hr, a mixture of two compounds was obtained. These were separated by column chromatography to give the two regio isomers **24** and **25**, resulting from attack at either the primary or secondary position of **18**. Reaction of **18** in the presence of dibenzyl hydrogen phosphate at -18°C for *ca* 3 hr changed the product ratio from 1:1 (at room temperature) to *ca* 4:1. The benzyl groups were removed by catalytic hydrogenolysis (H_2, Pd/C), and the products were subsequently converted into their corresponding pure di-sodium salts, **30** and **31**, by passage of aqueous solutions of the deprotected products through an ion-exchange column (Dowex-50Wx2, sodium form). The acylated aziridines **19** and **20** were then treated in a similar manner to yield compounds **26/27** (9:2) and **28/29** (5:1). They were also converted into the corresponding pure di-sodium salts **32-35** as described.



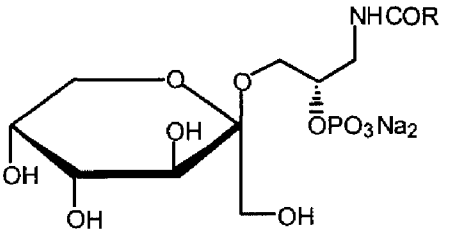
24 R=$C_{11}H_{23}$
26 R=$C_{13}H_{27}$
28 R=$C_{15}H_{31}$



25 R =$C_{11}H_{23}$
27 R =$C_{13}H_{27}$
29 R =$C_{15}H_{31}$

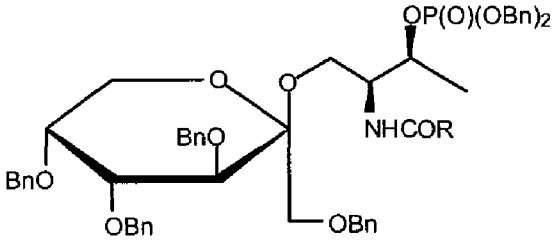


30 R=$C_{11}H_{23}$ (52.8%)
32 R=$C_{13}H_{27}$ (56.5%)
34 R=$C_{15}H_{31}$ (65%)

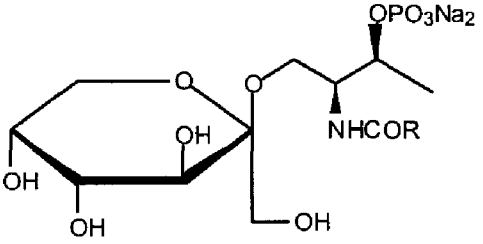


31 R=$C_{11}H_{23}$ (52.7%)
33 R=$C_{13}H_{27}$ (45%)
35 R=$C_{15}H_{31}$ (50%)

Further investigations on the acid catalyzed ring opening by dibenzyl hydrogen phosphate were then performed on derivatives in which the *N*-acyl aziridine ring was situated between two secondary carbon atoms (i.e. two chiral centres). Unlike the reactions of compounds **18-20** with dibenzyl hydrogen phosphate, which furnished two isomer derivatives, treatment of the N-acyl aziridines **21**, **22**, and **23** (see Chapter 6) yielded only one diastereoisomer in each case. These observations were supported by ^{31}P-NMR spectroscopy which indicated a singlet for a phosphate group at approximately -3.5 ppm in each case. These products resulted from ring-opening by dibenzyl phosphate at the C-3 position of the *N*-acyl aziridines **21**, **22**, and **23**. This was confirmed by the position of the amide functionality in the structures of compounds **36**, **37**, and **38** deduced by ^{1}H-NMR spectroscopy on the products obtained, irradiated at δ = 4.07 ppm (H-2). The position of the amide functionality at C-2 was also confirmed by (H,H)-COSY spectroscopy, which indicated a coupling between the proton in the amide functionality and H-2. (see Chapter 6).



36 R=$C_{11}H_{23}$ (72.3%)
37 R=$C_{13}H_{27}$ (70%)
38 R=$C_{15}H_{31}$ (75.0%)



39 R=$C_{11}H_{23}$ (70.8%)
40 R=$C_{13}H_{27}$ (72.4%)
41 R=$C_{15}H_{31}$ (69.2%)

7.3 Concluding remarks

The results described in this chapter show that aziridine derivatives derived from D-fructose can be readily prepared from the corresponding oxiranes or cyclic sulfates using simple procedures. The conversion of the oxiranes and the cyclic sulfates into the corresponding aziridine derivatives resulted in inversion of configuration at the respective chiral centres. Acylation of the aziridines was not only a convenient method for activating the aziridine ring, but also for the introduction of the long chain alkyl groups. Improvement of the regioselectivity of the nucleophilic ring opening reaction of the *N*-acyl compounds **18**, **19** and **20** using dibenzyl hydrogen phosphate as a nucleophile was obtained, when lower temperatures were applied during the reactions. Higher regioselectivity of nucleophilic ring opening of compounds **21**, **22** and **23** was also observed since only one regioisomer derivative was obtained from each reaction. These results show that the prepared aziridines can be used as basic units for the synthesis of several long-chain acylamino D-fructose phosphate derivatives as potential surfactant glycosides with chiral aglycon units.

7.4 Experimental section

General experimental procedures are given in Chapter 3.

*2(**R**)-Hydroxy-3-azidopropyl 1',3',4',5'-tetra*-O-*benzyl*-β-**D**-*fructopyranoside (**6**)*

Method A [26] (*via* oxirane **5**).

A stirred solution of the oxirane **5** (667 mg, 1.12 mmol) in a mixture of 2-methoxyethanol / water (20 mL, 3:1) was treated with sodium azide (291.2 mg, 4.48 mmol, 4.0 eq) and ammonium sulfate (591 mg, 4.48 mmol, 4.0 eq), and set aside at room temperature for 4 days. The mixture was treated with water (20 mL) and ether (50 mL), and the separated aqueous layer extracted with ether (2x25 ml). The combined organic layer was washed with aqueous sodium chloride solution (10%, 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (n-hexane-ethyl acetate, 2:1) of the crude material gave compound **6** (673 mg, 94%) as a pure colourless oil. $[\alpha]_D$ –42.2° ($CHCl_3$); MS (CI-CH_4) M/z 640 (M^++H), 523 (M^++H -$HOCH_2CH(OH)CH_2N_3$). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 138.39, 138.37, 138.31, 137.64, 128.28, 128.20, 128.09, 128.06, 127.9, 127.7, 127.6, 127.5, 127.4 (aromatic-C), 101.35(C-2), 78.5 (C-3), 77.3 (C-4), 75.6, 73.65 (benzylic-C), 73.20 (C-5), 71.99, 71.25 (benzylic-C), 70.12 (C-1), 69.63 (C-2'), 63.35 (C-1'), 61.2 (C-6), 53.0 (C-3') ppm. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.40-7.19 (m, 20H, aromatic H), 4.88, 4.60 (2d, 2H, J = 10.8 Hz, benzylic-H), 4.75, 4.70 (2d, 2H, J = 12.6 Hz, benzylic-H), 4.65, 4.45 (2d, 2H, J = 11.8 Hz, benzylic-H), 4.61, 4.58 (2d, 2H, J = 11.0 Hz, benzylic-H), 4.31 (d, 1H, J = 10.0 Hz, H-3), 3.92 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.2 Hz, H-4), 3.88 (dd, 1H, $J_{5,6eq}$ = 2.0 Hz, $J_{6ax,6eq}$ = -12.3 Hz, H-6eq), 3.85 (dd, 1H, $J_{5,6ax}$ = 1.9 Hz, $J_{6ax,6eq}$ = -12.3 Hz, H-6ax), 3.81 (m, 1H, H-2'), 3.79 (m, 1H, H-5), 3.77 (2d, 1H, J = -10.2 Hz, H-1a), 3.64 (2d, 1H, J = -10.2 Hz, H-1b), 3.49 (dd, 1H, J = 7.3 Hz, H-1'a), 3.46 (dd, 1H, J = 7.3 Hz, H-1'b), 3.25 (d, 1H, $J_{3'a,2'}$ = 3.6 Hz, H-3'a), 3.24 (d, 1H, $J_{3'b,2'}$ = 3.6 Hz, H-3'b), 2.0 (bs, 1H, O*H*) ppm.

Method B [25](*via* cyclic sulfate **9**).

A stirred solution of the cyclic sulfate **9** (480 mg, 0.71 mmol) in DMF (5 mL) was treated with lithium azide (63.9 mg, 1.42 mmol, 2.0 eq) at 80°C for 1 hr. The mixture was concentrated *in vacuo*, dissolved in freshly distilled tetrahydrofuran (10 mL), cooled (0°C), and a few drops of conc H_2SO_4 was added, and the mixture was set aside at room temperature for 15 mins. The reaction was then complete (TLC), and saturated aqueous sodium hydrogen carbonate was added, stirred for an extra 15 mins to neutralize the acid, and then treated with ether (20 mL). The separated organic layer was washed with 10% NaCl solution (20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Column chromatography (n-hexane-ethyl acetate, 1:1) of the residue gave compound **6** as a colourless oil (348 mg, 76.9%). $[\alpha]_D$ –42.3° ($CHCl_3$); the spectral characteristics were as described above.

*2(**R**)-p-Toluenesulfonyloxy-3-azidopropyl 1',3',4',5'-tetra-*O*-benzyl-β-**D**-fructopyranoside (7)*

A stirred, cooled (0°C) solution of compound **6** (1.040 g, 1.62 mmol) in dry pyridine (5 mL) was treated with *p*-toluenesulfonyl chloride (926.5 mg, 4.86 mmol, 3.0 eq) and set aside at room temperature for 24 hr. The reaction mixture was poured in ice water and left for 1 hr, diluted with dichloromethane (100 mL) and the separated organic layer washed, successively with aqueous hydrochloric acid (2**M**, 50 mL), water (50 mL) and saturated aqueous sodium hydrogen carbonate (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (n-hexane-ethyl acetate, 3:2) of the crude material gave **7** (1.1797 g, 92%) as a pure colourless oil. $[\alpha]_D$ –47.0° ($CHCl_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 138.08, 138.94, 138.44, 138.40, 137.77, 129.85, 128.29, 128.11, 127.88, 127.79, 127.75, 127.71, 127.68, 127.57, 127.49, 127.29 (aromatic-C), 101.64 (C-2), 78.29 (C-3), 76.57 (C-4), 76.19, 75.28 (benzylic-C), 73.63 (C-5), 73.40 (C-2'), 72.04, 71.22 (benzylic-C), 70.24 (C-1'), 64.73 (C-1), 61.36 (C-6), 50.83 (C-3'), and 21.61, 15.43 (CH_3) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.79-7.15 (m, 24H, aromatic H), 4.90 (d, 1H, J = 11.2 Hz, benzylic-H), 4.75, 4.69 (2d, 2H, J = 12.6 Hz, benzylic-H), 4.66-4.59 (m, 4H, benzylic-H), 4.43 (d, 1H, J = 11.9 Hz, benzylic-H), 4.28 (d, 1H, J = 10.0 Hz, H-3), 3.90, 3.88 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.1 Hz, H-4), 3.79-3.57 (m, 9H, H-1a, H-1b, H-1'a, H-1'b, H-2', H-3b', H-5, H-6eq, H-6ax), 3.39 (dd, 1H, J = 5.78 Hz, H-3'a), 2.39 (s, 3H, CH_3) ppm.

*2(**S**),3-Aziridinopropyl 1',3',4',5'-tetra-*O*-benzyl-β-**D**-fructopyranoside (8)*

A stirred, cooled (0°C) solution of **7** (1.1797 g, 1.487 mmol) in freshly distilled tetrahydrofuran (10 mL) was treated with lithium aluminium hydride (226.0 mg, 5.948 mmol, 4.0 eq). The reaction mixture was stirred at room temperature for 20-30 mins, quenched by addition of a mixture of ether (20 mL) and water (0.5 mL), filtered through $MgSO_4$, and the filtrate concentrated *in vacuo*. Column chromatography (dichloromethane-methanol, 9:1) of the crude product gave **8** (652.5mg, 68%) as a pure colourless oil. $[\alpha]_D$ –46.6° ($CHCl_3$); MS (CI-CH_4) M/z 596 (M^++H), 540 (M^++H –C_3H_6N), 523 (M^++H –C_3H_7ON). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 138.84, 138.68, 138.53, 138.00, 137.93, 128.25, 128.13, 127.75, 127.60, 127.44, 127.13 (aromatic-C), 101.40 (C-2), 78.33 (C-3), 76.43 (C-4), 75.59 (benzylic-C), 73.54 (C-5), 72.13, 71.17, 70.32 (benzylic-C), 70.25 (C-1'), 63.96 (C-1), 61.04 (C-6), 29.42 (C-2'), 22.56 (C-3') ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.40-7.23 (m, 20H, aromatic H), 4.92, 4.60 (2d, 2H, J =

11.2 Hz, benzylic-H), 4.75, 4.64 (2d, 2H, J = 12.6 Hz, benzylic-H), 4.64, 4.43 (2d, 2H, J = 11.9 Hz, benzylic-H), 4.35 (d, 1H, J = 10.1 Hz, H-3), 4.00 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.19 Hz, H-4), 3.83 (dd, 1H, $J_{5,6eq}$ = 1.7 Hz, $J_{6ax,6eq}$ = -12.3 Hz, H-6eq), 3.80 (dd, 1H, $J_{5,6ax}$=1.8 Hz, $J_{6ax,6eq}$ = -12.3 Hz, H-6ax), 3.80 (m, 1H, H-5), 3.74 (d, 1H, J=-10.1 Hz, H-1a), 3.60 (d, 1H, J = -10.1 Hz, H-1b), 2.20 (m, 1H, H-2'), 1.73 (dd, 1H, H-3a'), 1.31 (dd, 1H, H-3b') ppm.

*2(**R**)-Hydroxy-3-aminopropyl 1',3',4',5'-tetra*-O-*benzyl*-β-D-*fructopyranoside (14)*

A stirred solution of compound **6** (313 mg, 0.48 mmol) in toluene (2 mL) was treated with triphenylphosphine (251 mg, 0.96 mmol, 2.0 eq) at room temperature until evolution of nitrogen ceased and then heated at 70°C for 4 hr. The mixture was concentrated *in vacuo* and column chromatography of the residue (CH_2Cl_2-MeOH, 9:1) gave **14** (252.7 mg, 86.6%) as a pure colourless oil. $[\alpha]_D$ –52.0° ($CHCl_3$); MS (CI-CH_4) M/z 614 (M^++H), 536 (M^+ +H^+-C_6H_6), 523 (M^+ +H^+-$HOCH_2CH(OH)CH_2NH_2$). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 138.62, 138.50, 138.39, 137.82, 128.28, 128.18, 127.98, 127.87, 127.73, 127.65, 127.58, 127.48 (aromatic-C), 102.21 (C-2), 78.59 (C-3), 77.31 (C-4), 75.51, 73.62 (benzylic-C), 73.35 (C-5), 71.95, 71.19 (benzylic-C), 70.33 (C-1), 70.18 (C-2'), 64.53 (C-1'), 61.10 (C-6) and 44.11 (C-3') ppm. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.40-7.19 (m, 20H, aromatic H), 4.90, 4.60 (2d, 2H, J = 10.8 Hz, benzylic-H), 4.75, 4.70 (2d, 2H, J = 12.5 Hz, benzylic-H), 4.68, 4.45 (2d, 2H, J = 11.8 Hz, benzylic-H), 4.60, 4.58 (2d, 2H, J = 10.3 Hz, benzylic-H), 4.33 (d, 1H, J = 10.0 Hz, H-3), 3.94 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.2 Hz, H-4), 3.87 (dd, 1H, $J_{5,6eq}$ = 1.6 Hz, $J_{6ax,6eq}$ = -12.3 Hz, H-6eq), 3.84 (dd, 1H, $J_{5,6ax}$ = 1.5 Hz, $J_{6ax,6eq}$ = -12.3 Hz, H-6ax), 3.78 (m, 1H, H-2'), 3.77 (2d, 1H, J = -10.2 Hz, H-1a), 3.63 (2d, 1H, J = -10.2 Hz, H-1b), 3.66 (m, 1H, H-5), 3.52 (dd, 1H, J = 6.1 Hz, H-1'a), 3.35 (dd, 1H, J = 6.1 Hz, H-1'b), 2.67 (d, 1H, $J_{3'a,2}$ = 4.3 Hz, H-3'a), 2.59 (d, 1H, $J_{3'b,2}$ = 4.3 Hz, H-3'b), 2.4 (bs, 1H, O*H*) ppm.

*2(**S**),3-*N*-dodecanoyl aziridinopropyl 1',3',4',5'-tetra*-O-*benzyl*-β-D-*fructopyranoside (18)*

A stirred, cooled (–18°C) solution of **8** (401.3 mg, 0.674 mmol) in dichloromethane (5 mL) containing triethylamine (0.15 mL, 2.5 eq) was treated with lauroyl chloride (0.17 mL, 0.741 mmol, 1.1 eq) and set aside for 2 hr. The reaction mixture was then diluted with dichloromethane (10 mL) and washed with 10% (w / w), aqueous citric acid (10 mL) and the organic extract was dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (n-hexane-ethyl acetate, 3:1) of the resultant crude material gave **18** (403 mg, 77%) as a pure colourless oil. $[\alpha]_D$ –53.8° ($CHCl_3$). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 185.65 (*C*=O), 138.71, 138.48, 138.39, 137.81, 128.21, 128.07, 127.82, 127.72, 127.63, 127.47, 127.40, 127.32 (aromatic-C), 101.49 (C-2), 78.83 (C-3), 76.57 (C-4), 75.44 (benzylic-C), 73.60 (C-5), 73.52, 72.15, 71.21 (benzylic-C), 70.29 (C-1'), 62.76 (C-1), 61.15 (C-6), 36.48 (C-3'), 35.74 (C-2'), 31.82 ($COCH_2$), 29.54-22.60 (aliphatic C), and 14.06 (CH_3) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.41-7.23 (m, 20H, aromatic H), 4.93, 4.60 (2d, 2H, J = 11.2 Hz, benzylic-H), 4.77, 4.72 (2d, 2H, J = 12.6 Hz, benzylic-H), 4.64, 4.44 (2d, 2H, J = 11.9 Hz, benzylic-H), 4.34 (d, 1H, J = 10.0 Hz, H-3), 4.00 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.0 Hz, H-4), 3.88-3.81 (m, 3H, H-5, H-6), 3.76-3.58 (m, 4H, H-1a, H-1b H-1a', H-1b'), 3.46, 3.43 (dd, 1H, H-3'), 2.67-2.60 (m, 1H, H-2'), 2.34 (t, 2H, $COCH_2$), 1.55 (m, 2H, CH_2CH_3), 1.29 (m, 16H, aliphatic H), 0.87 (t, 3H, J = 6.7 Hz, CH_3) ppm.

*2(**S**),3-N-tetradecanoyl aziridinopropyl 1',3',4',5'-tetra-O-benzyl-β-**D**-fructopyranoside (**19**)*

Compound **19** was prepared from **8** (607 mg, 1.018 mmol) and myristic chloride (276.7 mg, 1.12 mmol, 1.1 eq) using the same procedure as described for the synthesis of compound **18**. Column chromatography (n-hexane-ethyl acetate, 3:1) of the crude product gave **19** (509 mg, 62.0%) as a pure colourless oil. $[\alpha]_D$ –51.2° ($CHCl_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 185.50 (*C*=O), 138.85, 138.63, 138.49, 137.69, 128.30, 128.19, 128.03, 127.95, 127.86, 127.68, 127.52, 127.44, 127.35 (aromatic-C), 101.08 (C-2), 78.54 (C-3), 76.72 (C-4), 75.72 (benzylic-C), 73.73 (C-5), 73.42, 72.26, 71.28 (benzylic-C), 70.33 (C-1'), 61.61 (C-1), 61.17 (C-6), 36.26 (C-3'), 34.27 (C-2'), 31.87 ($COCH_2$), 29.60-22.64 (aliphatic C), and 14.07 (CH_3) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.41-7.23 (m, 20H, aromatic H), 4.92, 4.61 (2d, 2H, J = 11.2 Hz, benzylic-H), 4.77, 4.72 (2d, 2H, J = 12.6 Hz, benzylic-H), 4.64, 4.44 (2d, 2H, J = 11.9 Hz, benzylic-H), 4.33 (d, 1H, J = 10.0 Hz, H-3), 4.01 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.0 Hz, H-4), 3.87-3.81 (m, 3H, H-5, H-6), 3.76-3.59 (m, 4H, H-1a, H-1b, H-1a', H-1b'), 3.45, 3.43 (dd, 1H, H-3'), 2.67-2.60 (m, 1H, H-2'), 2.34 (t, 2H, $COCH_2$), 1.55 (m, 2H, CH_2CH_3), 1.29 (m, 20H, aliphatic H), 0.87 (t, 3H, J = 6.7 Hz, CH_3) ppm.

*2(**S**),3-N-hexadecanoylaziridinopropyl 1',3',4',5'-tetra-O-benzyl-β-**D**-fructopyranoside (**20**)*

Compound **20** was prepared starting from **8** (555 mg, 0.93 mmol) and palmitoyl chloride, (281.3 mg, 1.023 mmol, 1.1 eq) using the same procedure as described for the synthesis of compound **18**. Column chromatography (n-hexane-ethyl acetate, 3:1) of the resultant crude material gave **20** (615 mg, 79%) as a pure colourless oil. $[\alpha]_D$ –54.8° ($CHCl_3$). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 185.73 (C=O), 138.74, 138.63, 138.47, 137.80, 128.24, 128.08, 127.82, 127.73, 127.64, 127.48, 127.42, 127.33 (aromatic-C), 101.66 (C-2), 78.99 (C-3), 76.35 (C-4), 75.53 (benzylic-C), 73.88 (C-5), 73.66, 72.30, 71.41 (benzylic-C), 70.46 (C-1'), 62.83 (C-1), 61.35 (C-6), 36.60 (C-3'), 35.89 (C-2'), 31.94 ($COCH_2$), 29.65-22.71 (aliphatic C), and 14.15 (CH_3) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.41-7.23 (m, 20H, aromatic H), 4.91, 4.60 (2d, 2H, J = 11.2 Hz, benzylic-H), 4.76, 4.70 (2d, 2H, J = 12.6 Hz, benzylic-H), 4.63, 4.44 (2d, 2H, J = 11.9 Hz, benzylic-H), 4.32 (d, 1H, J = 10.0 Hz, H-3), 4.02 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.0 Hz, H-4), 3.87-3.81 (m, 3H, H-5, H-6), 3.76-3.59 (m, 4H, H-1, H-1'), 3.45, 3.43 (dd, 1H, H-3'), 2.68-2.61 (m, 1H, H-2'), 2.34 (t, 2H, $COCH_2$), 1.55 (m, 2H, CH_2CH_3), 1.30(m, 24H, aliphatic H), 0.87 (t, 3H, J = 6.7 Hz, CH_3) ppm.

*3-Dibenzyl-2(**S**)-dodecanoylamidopropyl 1',3',4',5'-tetra-O-benzyl-β-**D**-fructopyranoside-3-phosphate (**24**) and (2**S**)-Dibenzyl-3-dodecanoylamidopropyl 1',3',4',5'-tetra-O-benzyl-β-**D**-fructopyranoside-2-phosphate (**25**)*

A stirred, cooled (–18°C) solution of **18** (742.7 mg, 0.954 mmol) in dichloromethane (5 mL) was treated with dibenzyl hydrogen phosphate (318 mg, 1.145 mmol, 1.2 eq) and set aside for 1 hr. The reaction mixture was diluted with dichloromethane (20 mL), washed with saturated aqueous sodium hydrogen carbonate (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The two regioisomers were separated by column chromatography (n-heptane-ethyl acetate, 1:1) to give compounds **24** (458.7 mg, 45.5%) $[\alpha]_D$ –30.3° ($CHCl_3$) and **25** (102 mg, 10.1%) $[\alpha]_D$ – 42.0° ($CHCl_3$) as pure colourless oils. When the reaction of **18** (400 mg, 0.513 mmol) with

dibenzyl hydrogen phosphate (171.2 mg, 0.616 mmol, 1.2 eq) was performed at room temperature for 2 hr, compounds **24** and **25** were isolated in a 1:1 ratio.

Compound **24** ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 173.00 (*C*=O), 138.86, 138.43, 137.75, 135.56, 135.49, 128.67, 128.58, 128.56, 128.43, 128.34, 128.24, 128.21, 128.08, 128.04, 128.02, 127.91, 127.88, 127.76, 127.65, 127.62, 127.55, 127.49, 127.42, 127.35 (aromatic-C), 101.06 (C-2), 78.51 (C-3), 77.31 (C-4), 76.62, 75.26 (benzylic-C), 73.61 (C-5), 73.27, 71.75, 71.16 , 70.28 (benzylic-C), 69.48 (C-1'), 69.43 (C-1), 61.18 (C-6), 58.85 (C-3'), 48.34 (C-2'), 36.25 ($COCH_2$), 31.84-22.61 (aliphatic C), and 14.05 (CH_3) ppm. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.38-7.19 (m, 30H, aromatic H), 6.52 (d, 1H, J = 8.3 Hz, N*H*CO), 5.00-4.96 (m, 4H, benzylic-H), 4.90 (d, 1H, J = 11.0 Hz benzylic-H), 4.70, 4.65 (2d, 2H, J = 12.5 Hz, benzylic-H), 4.61-4.56 (m, 4H, benzylic-H), 4.36 (d, 1H, J = 11.8 Hz, benzylic-H), 4.29 (d, 1H, J = 10.0 Hz, 3), 3.98 (m, 1H, H-2'), 3.88, 3.86 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.15 Hz, H-4), 3.82 (dd, 1H, $J_{5,6eq}$ = 1.7Hz, $J_{6ax,6eq}$ = -12.5 Hz, H-6eq), 3.79 (dd, 1H, $J_{5,6ax}$ = 1.6 Hz, $J_{6ax,6eq}$ = -12.5 Hz, H-6ax), 3.72 (m, 1H, H-5), 3.70 (d, 1H, J = -10.1 Hz, H-1a), 3.66 (dd, 1H, J = 5.0 Hz, H-3'b), 3.58 (d, 1H, J = -10.1 Hz, H-1b), 3.48 (d, 1H, $J_{1'a,2'}$ = 7.0 Hz, H-1'a), 3.45 (d, 1H, $J_{1'b,2'}$ = 7.0 Hz, H-1'b), 3.40 (dd, 1H, J = 5.0Hz, H-3a'), 1.84-1.92(t, 2H, $COCH_2$), 1.48 (m, 2H, CH_2CH_3), 1.31-1.18 (m, 16H, aliphatic H), 0.87(t, 3H, CH_3) ppm.

Compound **25** ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 173.54 (*C*=O), 138.67, 138.45, 138.41, 138.31, 138.20, 137.80, 137.75, 128.58, 128.50, 128.39, 128.35, 128.28, 128.12, 128.00, 127.94, 127.88, 127.82, 127.71, 127.66, 127.47 (aromatic-C), 101.31 (C-2), 78.38 (C-3), 76.68 (C-4), 76.53, 75.60 (benzylic-C), 73.66 (C-5), 71.80, 71.18, 70.32 (benzylic-C), 69.60 (C-2'), 69.54 (benzylic-C), 69.49 (C-1'), 68.51 (C-1), 61.19 (C-6), 60.40 (C-3'), 39.77 ($COCH_2$), 31.87-22.65 (aliphatic C), and 14.08 (CH_3) ppm. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.37-7.17 (m, 30H, aromatic H), 5.80 (t, 1H, J = 5.6 Hz, N*H*CO), 5.00-4.96 (m, 4H, benzylic-H), 4.90 (d, 1H, J = 11.0 Hz, benzylic-H), 4.75, 4.68 (2d, 2H, J = 12.5 Hz, benzylic-H), 4.65-4.51 (m, 6H, benzylic-H), 4.45 (d, 1H, J = 10.0 Hz, H-3), 3.95, 3.82 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.0 Hz, H-4), 3.82 (dd, 1H, $J_{5,6eq}$ = 1.7 Hz, $J_{6ax,6eq}$ = -12.5 Hz, H-6eq), 3.79 (dd, 1H, $J_{5,6ax}$ = 1.6 Hz, $J_{6ax,6eq}$ = -12.5 Hz, H-6ax), 3.72 (m, 1H, H-5), 3.68 (d, 1H, J = -10.1 Hz, 1H-a), 3.47 (dd, 1H, J = 5.0 Hz, H-3'b), 3.58 (d, 1H, J = -10.1 Hz, H-1b), 3.48 (d, 1H, H-1'a), 3.45 (d, 1H, H-1'b), 3.12 (dd, 1H, J = 5.0 Hz, H-3a'), 1.84-1.92 (t, 2H, $COCH_2$), 1.48 (m, 2H, CH_2CH_3), 1.31-1.18 (m, 16H, aliphatic H), 0.87 (t, 3H, CH_3) ppm.

*3-Dibenzyl-2(**S**)-tetradecanoylamidopropyl 1',3',4',5'-tetra-O-benzyl-β-**D**-fructopyranoside-3-phosphate (26) and 2(**R**)-Dibenzyl-3-tetradecanoylamidopropyl 1',3',4',5'-tetra-O-benzyl-β-**D**-fructopyranoside-2-phosphate (27)*

A stirred, cooled (–18°C) solution of **19** (469.5 mg, 0.582 mmol) in dichloromethane (5 mL) was treated with dibenzyl hydrogen phosphate (194 mg, 0.64 mmol, 1.2 eq) and set aside for 1 hr. The reaction mixture was diluted with dichloromethane (20 mL), washed with saturated aqueous sodium hydrogen carbonate (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The two regioisomers were separated by column chromatography (n-heptane-ethyl acetate, 1:1) to

give compounds **26** (260 mg, 41.2%), $[\alpha]_D$ –31.8° ($CHCl_3$) and **27** (67 mg, 10.6%), $[\alpha]_D$ –32.3° ($CHCl_3$) as pure colourless oils. When the reaction of **19** (250 mg, 0.309 mmol) with dibenzyl hydrogen phosphate (112 mg, 0.371 mmol, 1.2 eq) was performed at room temperature for 2 hr, compounds **26** and **27** were isolated in a 1:1 ratio.

Compound **26** ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 172.96 (*C*=O), 138.89, 138.41, 137.73, 135.55, 135.46, 128.57, 128.24, 128.08, 128.43, 128.34, 127.90, 127.77, 127.71, 127.63, 127.55, 127.43, 127.33 (aromatic-C), 101.05 (C-2), 78.51 (C-3), 77.42 (C-4), 76.59, 75.23 (benzylic-C), 73.60 (C-5), 73.22, 71.75, 71.13 (benzylic-C), 70.27 (benzylic-C), 69.49 (C-1'), 69.42 (C-1), 61.16 (C-6), 58.81 (C-3'), 48.37 (C-2'), 36.26 (CO*C*H_2), 31.85-22.62 (aliphatic C), and 14.07 (*C*H_3) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.39-7.22 (m, 30H, aromatic H), 6.45 (d, 1H, J = 8.3 Hz, N*H*CO), 5.00-4.95 (m, 4H, benzylic-H), 4.90 (d, 1H, J = 11.0 Hz benzylic-H), 4.72, 4.66 (2d, 2H, J = 12.6 Hz, benzylic-H), 4.63-4.55 (m, 4H, benzylic-H), 4.42 (d, 1H, J = 11.8 Hz, benzylic-H), 4.29 (d, 1H, J = 10.0 Hz, H-3), 4.20 (m, 1H, H-2'), 3.88, 3.85 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.0 Hz, H-4), 3.83 (dd, 1H, $J_{5,6eq}$ = 1.7 Hz, $J_{6ax,6eq}$ = -12.5 Hz, H-6eq), 3.79 (dd, 1H, $J_{5,6ax}$ = 1.6 Hz, $J_{6ax,6eq}$ = -12.5 Hz, H-6ax), 3.73 (m, 1H, H-5), 3.71 (d, 1H, J = -10.1 Hz, H-1a), 3.65 (dd, 1H, J = 5.2 Hz, H-3'b), 3.63 (d, 1H, J = -10.1 Hz, H-1b), 3.58 (d, 1H, H-1'a), 3.54 (d, 1H, H-1'b), 3.39 (dd, 1H, J = 5.2 Hz, H-3a'), 1.94-1.89 (t, 2H, COCH_2), 1.48 (m, 2H, CH_2CH$_3$), 1.32-1.24 (m, 20H, aliphatic H), 0.87 (t, 3H, CH_3) ppm.

Compound **27** ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 173.14(*C*=O), 138.65, 138.42, 138.38, 138.29, 138.26, 137.78, 137.75, 135.49, 135.46, 128.57, 128.52, 128.38, 128.34, 127.80, 127.76, 127.64, 127.48 (aromatic-C), 101.29 (C-2), 78.48 (C-3), 76.66 (C-4), 76.52, 75.60 (benzylic-C), 73.65 (C-5), 71.82, 71.18, 70.34 (benzylic-C), 69.59 (C-2'), 69.51 (benzylic-C), 69.48 (C-1'), 68.51 (C-1), 61.19 (C-6), 60.40 (C-3'), 39.77 (CO*C*H_2), 31.87-22.65(aliphatic C), and 14.07 (*C*H_3) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.39-7.18 (m, 30H, aromatic H), 5.82 (t, 1H, J = 5.6 Hz, N*H*CO), 5.01-4.95 (m, 4H, benzylic-H), 4.90 (d, 1H, J = 11.0 Hz, benzylic-H), 4.73, 4.67 (2d, 2H, J = 12.5 Hz, benzylic-H), 4.65-4.51 (m, 6H, benzylic-H), 4.45 (d, 1H, J = 10.0 Hz, H-3), 3.95, 3.82 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.0 Hz, H-4), 3.82 (dd, 1H, $J_{5,6eq}$ = 1.7 Hz, $J_{6ax,6eq}$ = -12.5 Hz, H-6eq), 3.79 (dd, 1H, $J_{5,6ax}$ = 1.6 Hz, $J_{6ax,6eq}$ = -12.5 Hz, H-6ax), 3.71 (m, 1H, H-5), 3.66 (d, 1H, J = -10.1 Hz, H-1a), 3.47 (dd, 1H, J = 5.0 Hz, H-3'b), 3.58 (d, 1H, J = -10.1 Hz, H-1b), 3.48 (d, 1H, H-1'a), 3.44 (d, 1H, H-1'b), 3.12 (dd, 1H, J = 5.0 Hz, H-3a'), 1.84-1.93 (t, 2H, COCH_2), 1.47 (m, 2H, CH_2CH$_3$), 1.31-1.19 (m, 20H, aliphatic H), 0.87 (t, 3H, CH_3) ppm.

*3-Dibenzyl-2(***S***)-hexadecanoylamidopropyl 1',3',4',5'-tetra-*O*-benzyl-*β*-***D***-fructopyranoside-3-phosphate (**28**) and 2(***R***)-Dibenzyl-3-hexadecanoylamidopropyl 1',3',4',5'-tetra-*O*-benzyl-*β*-***D***-fructopyranoside-2-phosphate (**29**)*

A stirred, cooled (–18°C) solution of **20** (404 mg, 0.484 mmol) in dichloromethane (5 mL) was treated with dibenzyl hydrogen phosphate (161.6 mg, 0.580 mmol, 1.2 eq) and set aside for 1 hr. The reaction mixture was diluted with dichloromethane (20 mL), washed with saturated aqueous sodium hydrogen carbonate (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The two regioisomers were separated by column chromatography (n-heptane-ethyl

acetate, 1:1) to give compounds **28** (279 mg, 51.8%), $[\alpha]_D$ –31.4° ($CHCl_3$) and **29** (40 mg, 7.4%), $[\alpha]_D$ –33.6° ($CHCl_3$) as pure colourless oils. When the reaction of **20** (202 mg, 0.242 mmol) with dibenzyl hydrogen phosphate (80.9 mg, 0.290 mmol, 1.2 eq was performed at room temperature for 2 hr, compounds **28** and **29** were isolated in a 1:1 ratio.

Compound **28** ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 172.78 (*C*=O), 138.85, 138.42, 137.69, 135.50, 135.48, 128.55, 128.23, 128.07, 128.44, 128.36, 127.91, 127.76, 127.70, 127.63, 127.50, 127.43, 127.33 (aromatic-C), 101.04 (C-2), 78.51 (C-3), 77.44 (C-4), 76.58, 75.25 (benzylic-C), 73.62 (C-5), 73.21, 71.75, 71.15, 70.27 (benzylic-C), 69.48 (C-1'), 69.43 (C-1), 61.16 (C-6), 58.80 (C-3'), 48.38 (C-2'), 36.26 ($COCH_2$), 31.85-22.62 (aliphatic C), and 14.07 (CH_3) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.39-7.23 (m, 30H, aromatic H), 6.44 (d, 1H, J = 8.3 Hz, N*H*CO), 5.00-4.95 (m, 4H, benzylic-H), 4.91 (d, 1H, J = 11.0 Hz, benzylic-H), 4.73, 4.66 (2d, 2H, J = 12.6 Hz, benzylic-H), 4.63-4.54 (m, 4H, benzylic-H), 4.43 (d, 1H, J = 11.8 Hz, benzylic-H), 4.27 (d, 1H, J = 10.0 Hz, H-3), 4.22 (m, 1H, H-2'), 3.88, 3.85 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.0 Hz, H-4), 3.83 (dd, 1H, $J_{5,6eq}$ = 1.7 Hz, $J_{6ax,6eq}$ = -12.5 Hz, H-6eq), 3.79 (dd, 1H, $J_{5,6ax}$ = 1.6 Hz, $J_{6ax,6eq}$ = -12.5 Hz, H-6ax), 3.73 (m, 1H, H-5), 3.70 (d, 1H, J = -10.1 Hz, H-1a), 3.65 (dd, 1H, J = 5.2 Hz, H-3'b), 3.63 (d, 1H, J = -10.1 Hz, H-1b), 3.58 (d, 1H, H-1'a), 3.54 (d, 1H, H-1'b), 3.38 (dd, 1H, J = 5.2 Hz, H-3a'), 1.94-1.89 (t, 2H, COCH_2), 1.48 (m, 2H, CH_2CH$_3$), 1.32-1.24 (m, 24H, aliphatic H), 0.87 (t, 3H, CH_3) ppm.

Compound **29** ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 173.16 (*C*=O), 138.64, 138.46, 138.37, 138.26, 138.24, 137.75, 137.78, 135.54, 135.49, 128.53, 128.52, 128.37, 128.33, 127.79, 127.75, 127.64, 127.46 (aromatic-C), 101.27 (C-2), 78.45 (C-3), 76.67 (C-4), 76.52, 75.60 (benzylic-C), 73.64 (C-5), 71.79, 71.16, 70.34 (benzylic-C), 69.58 (C-2'), 69.51 (benzylic-C), 69.47 (C-1'), 68.51 (C-1), 61.19 (C-6), 60.39 (C-3'), 39.76 ($COCH_2$), 31.87-22.65 (aliphatic C), and 14.06 (CH_3) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.40-7.20 (m, 30H, aromatic H), 5.81 (t, 1H, J = 5.6 Hz, N*H*CO), 5.01-4.94 (m, 4H, benzylic-H), 4.91 (d, 1H, J = 11.0 Hz, benzylic-H), 4.72, 4.68 (2d, 2H, J = 12.5 Hz, benzylic-H), 4.65-4.51 (m, 5H, benzylic-H), 4.44 (d, 1H, J = 10.0 Hz, H-3), 3.94, 3.82 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.0 Hz, H-4), 3.80 (dd, 1H, $J_{5,6eq}$ = 1.7 Hz, $J_{6ax,6eq}$ = -12.5 Hz, H-6eq), 3.79 (dd, 1H, $J_{5,6ax}$ = 1.6 Hz, $J_{6ax,6eq}$ = -12.5 Hz, H-6ax), 3.71 (m, 1H, H-5), 3.65 (d, 1H, J = -10.1 Hz, H-1a), 3.46 (dd, 1H, J = 5.0 Hz, H-3'b), 3.58 (d, 1H, J = -10.1 Hz, H-1b), 3.48 (d, 1H, H-1'a), 3.43 (d, 1H, H-1'b), 3.12 (dd, 1H, J = 5.0 Hz, H-3a'), 1.83-1.92 (t, 2H, COCH_2), 1.47 (m, 2H, CH_2CH$_3$), 1.30-1.19 (m, 24H, aliphatic H), 0.87 (t, 3H, CH_3) ppm.

*3-Disodium 2(**S**)-dodecanoylamidopropyl-β-**D**-fructopyranoside-3-phosphate (**30**)*

A solution of compound **24** (286 mg, 0.27 mmol) in methanol (30 mL) containing palladium on charcoal (10%, 60 mg) was subjected to hydrogenation at room temperature for 2hr. The catalyst was removed by filtration, washed with methanol, and the combined filtrate and washings partially concentrated *in vacuo*. Water (10 mL) was added to the residue, and the mixture was then passed through an ion-exchange column (Dowex 50Wx2, sodium form). The methanol remaining in the eluate was removed *in vacuo,* and the resultant mixture was lyophilized to give **30** (80 mg, 52.8%) as white crystals. m.p. 150°C; $[\alpha]_D$ –46.0° (MeOH); MS

(FAB-Na^+) M/z 582 (M^++ Na^+), 398 (M^++ Na^+-$HCOC_{11}H_{23}$). ^{13}C-NMR (D_2O, 75 MHz) δ 176.89 (*C*=O), 101.87 (C-2), 70.86 (C-3), 70.58 (C-4), 69.57 (C-5), 65.37 (C-1), 64.31 (C-3'), 62.51 (C-1'), 60.79 (C-6), 50.29 (C-2'), 37.17 (-CO*C*H_2), 33.23-23.91 (aliphatic C) and 15.17 (*C*H_3) ppm. ^{1}H-NMR (D_2O, 400 MHz) δ 6.2 (d, 1H, N*H*CO), 4.25 (m, 1H, 2'), 4.03-3.75 (m, 8H, H-1a', H-1, H-3, H-4, H-5, H-6), 3.74-3.58 (m, 3H, H-1b', H-3'), 2.28 (t, 2H, COCH_2), 1.62 (m, 2H, $CH_2CH_2CH_3$), 1.33 (m, 16H, aliphatic H), and 0.80 (t, 3H, J = 6.7 Hz, CH_3) ppm. *Anal* calc for $C_{21}H_{40}NNa_2O_{11}P$: C 44.78; H 7.22; N 2.49. Found: C 44.84; H 6.97, N 2.30%.

*2(**R**)-Disodium 3-dodecanoylamidopropyl-β-**D**-fructopyranoside-2-phosphate (31)*

Compound **31** (40.5 mg, 52.7%) was prepared from **25** (145 mg, 0.137 mmol) under the same conditions described for the synthesis of compound **30**. m.p. 160°C; $[\alpha]_D$ –53.7° (MeOH); MS (FAB-Na^+) M/z 582 (M^++ Na^+), 398 (M^++ Na^+-$HCOC_{11}H_{23}$). ^{13}C-NMR (D_2O, 75 MHz) δ 176.80 (*C*=O), 101.78 (C-2), 70.84 (C-3), 70.57 (C-4), 69.56 (C-5), 65.38 (C-1), 65.12 (C-2'), 62.49 (C-1'), 60.67 (C-6), 50.44 (C-3'), 37.16 (-CO*C*H_2), 33.24-23.90 (aliphatic C) and 15.19 (*C*H_3) ppm. ^{1}H-NMR (D_2O, 400 MHz) δ 6.1 (t, 1H, N*H*CO), 4.03-3.75 (m, 9H, H-1, H-1a', H-2', H-3, H-4, H-5, H-6), 3.74-3.58 (m, 3H, H-1b', H-3'), 2.24 (t, 2H, COCH_2), 1.63 (m, 2H, $CH_2CH_2CH_3$), 1.32 (m, 16H, aliphatic H), and 0.80 (t, 3H, J = 6.7 Hz, CH_3) ppm. *Anal* calc for $C_{21}H_{40}NNa_2O_{11}P$: C 44.78; H 7.22; N 2.49. Found: C 44.93; H 6.92, N 2.42%.

*3-Disodium, 2(**S**)-tetradecanoylamidopropyl β-**D**-fructopyranoside-3-phosphate (32)*

Compound **26** (150 mg, 0.138 mmol) was treated under the above conditions to give **32** (46 mg, 56.6%) as white crystals. m.p. 175°C; $[\alpha]_D$ –46.8° (MeOH); MS (FAB-Na^+) M/z 611 (M^++ Na^+), ^{13}C-NMR (D_2O, 75 MHz) δ 176.11 (*C*=O), 101.62 (C-2), 71.40 (C-3), 71.14 (C-4), 70.86 (C-5), 65.42 (C-1), 63.37 (C-3'), 62.51 (C-1'), 60.86 (C-6), 51.23 (C-2'), 37.22 (-CO*C*H_2), 33.06-23.72 (aliphatic C) and 14.43 (*C*H_3) ppm. ^{1}H-NMR (D_2O, 400 MHz) δ 6.0(d, 1H, N*H*CO), 4.08 (m, 1H, 2'), 3.92-3.79 (m, 8H, H-1, H-1a', H-3, H-4, H-5, H-6), 3.78-3.61 (m, 3H, H-1b', H-3'), 2.21 (t, 2H, J = 7.6 Hz, COCH_2), 1.60 (m, 2H, $CH_2CH_2CH_3$), 1.28 (m, 20H, aliphatic H), and 0.89 (t, 3H, J = 6.8 Hz, CH_3) ppm. *Anal* calc for $C_{23}H_{44}NNa_2O_{11}P$: C 47.02; H 7.55; N 2.38. Found: C 46.82; H 7.40, N 2.16%.

*2(**R**)-Disodium, 3-tetradecanoylamidopropyl β-**D**-fructopyranoside-2-phosphate (33)*

Compound **27** (121 mg, 0.111 mmol) was treated in a similar manner to give **33** (29.5 mg, 45%) as white crystals. m.p. 180°C; $[\alpha]_D$ –54.3° (MeOH); MS (FAB-Na^+) M/z 611 (M^++ Na^+), ^{13}C-NMR (D_2O, 75 MHz) δ 176.22(*C*=O), 101.57 (C-2), 71.46 (C-3), 71.19 (C-4), 70.86 (C-5), 65.37 (C-1), 64.12 (C-2'), 62.34 (C-1'), 60.78 (C-6), 54.43 (C-3'), 37.21 (-CO*C*H_2), 33.06-23.72 (aliphatic C) and 14.43 (*C*H_3) ppm. ^{1}H-NMR (D_2O, 400 MHz) δ 6.0 (t, 1H, N*H*CO), 3.89-3.76 (m, 8H, H-1, H-1a', H-2', H-3, H-4, H-5, H-6), 3.75-3.60 (m, 3H, H-1b', H-3'), 2.19 (t, 2H, J = 7.6 Hz, COCH_2), 1.59 (m, 2H, $CH_2CH_2CH_3$), 1.26 (m, 20H, aliphatic H), and 0.89 (t, 3H, J = 6.8 Hz, CH_3) ppm. *Anal* calc for $C_{23}H_{44}NNa_2O_{11}P$: C 47.02; H 7.55; N 2.38. Found: C 46.74; H 7.33, N 2.15%.

*3-Disodium, 2(**S**)-hexadecanoylamidopropyl* β-**D**-*fructopyranoside-3-phosphate (**34**)*

Compound **28** (206 mg, 0.185 mmol) was treated in a similar fashion to give **34** (75 mg, 65%) as white crystals. m.p. 140°C; $[\alpha]_D$ –47.5° (MeOH); MS (FAB-Na^+) M/z 639 (M^++ Na^+), 400 (M^++ Na^+-$COC_{15}H_{31}$). ^{13}C-NMR (D_2O, 75 MHz) δ 177.92 (*C*=O), 101.77 (C-2), 70.82 (C-3), 70.46 (C-4), 69.67 (C-5), 65.27 (C-1), 64.40 (C-3'), 62.55 (C-1'), 61.41 (C-6), 50.68 (C-2'), 37.15 (-CO*C*H2), 32.75-23.54 (aliphatic C) and 14.89 (*C*H_3) ppm. ^{1}H-NMR (D_2O, 400 MHz) δ 6.1 (t, 1H, N*H*CO), 4.02-3.75 (m, 9H, H-1, H-1a', H-2', H-3, H-4, H-5, H-6), 3.71-3.62 (m, 3H, H-1b', H-3'), 2.30 (t, 2H, J = 7.5 Hz, COCH_2), 1.63 (m, 2H, $CH_2CH_2CH_3$), 1.34 (m, 24H, aliphatic H), and 0.91 (t, 3H, J = 6.8 Hz CH_3) ppm. *Anal* calc for $C_{25}H_{48}NNa_2O_{11}P$: C 48.78; H 7.86; N 2.28. Found: C 48.46; H 7.56, N 2.54%.

*2(**R**)-Disodium 3-hexadecanoylamidopropyl* β-**D**-*fructopyranoside-2-phosphate (**35**)*

Compound **29** (286 mg, 0.257 mmol) likewise gave **35** (79.2 mg, 50%) as white crystals. m.p. 155°C; $[\alpha]_D$ –56.5° (MeOH); MS (FAB-Na^+) M/z 639 (M^++ Na^+), 400 (M^++ Na^+-$COC_{15}H_{31}$). ^{13}C-NMR (D_2O, 75 MHz) δ 177.90 (*C*=O), 101.75 (C-2), 70.80 (C-3), 70.44 (C-4), 69.68 (C-5), 65.25 (C-1), 64.20 (C-2'), 62.50 (C-1'), 61.39 (C-6), 50.78 (C-3'), 37.17 (-COCH_2), 32.75-23.53 (aliphatic C) and 14.90 (*C*H_3) ppm. ^{1}H-NMR (D_2O, 400 MHz) δ 6.1 (t, 1H, N*H*CO), 4.04-3.74 (m, 9H, H-1, H-1a', H-2', H-3, H-4, H-5, H-6), 3.71-3.64 (m, 3H, H-1b', H-3',), 2.31 (t, 2H, J = 7.5 Hz, COCH_2), 1.64 (m, 2H, $CH_2CH_2CH_3$), 1.33 (m, 24H, aliphatic H), and 0.91 (t, 3H, J = 6.8 Hz, CH_3) ppm. *Anal* calc for $C_{25}H_{48}NNa_2O_{11}P$: C 48.78; H 7.86; N 2.28. Found: C 48.76; H 7.81, N 2.32%.

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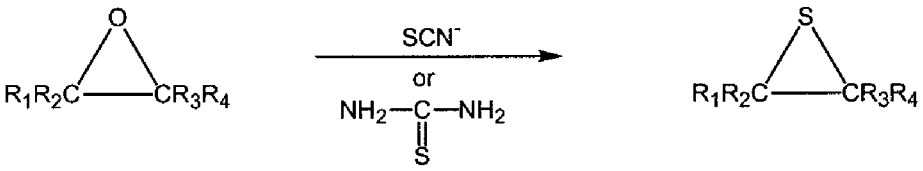
CHAPTER 8

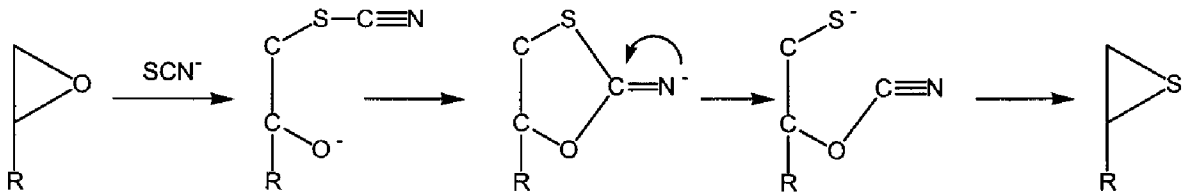
SYNTHESIS OF SOME EPITHIOALKYL DERIVATIVES OF D-FRUCTOSE

8.1 Introduction

Thiiranes (episulfide) are versatile organo-sulfur derivatives.[1-4] A wide variety of synthetic procedures have been described for their preparation. The reaction of oxiranes with thiocyanate ions or with thiourea seems, however, to be the most general approach (Scheme 8.1). These reactions have been applied to a wide range of thiirane compounds including, *inter alia* a number of carbohydrate derivatives.[5-7]

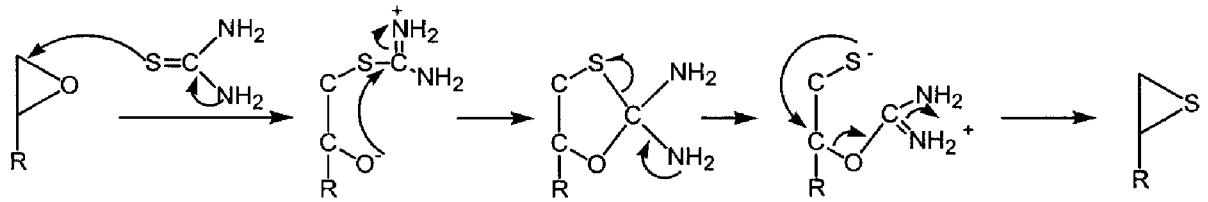


A simple mechanism for the reaction of oxiranes with thiocyanate ions is generally accepted.[1-4] It is based on the generation of a negatively charged thio (S^-) group, which is a powerful, intramolecular displacing function, *via* a five membered cyclic intermediate (Schemes 8.1). It is a *trans-trans* process, so there is a net overall inversion of configuration on replacement of oxygen by sulfur.



Scheme 8.1: Proposed mechanism for the synthesis of thiiranes via oxiranes using thiocyanate

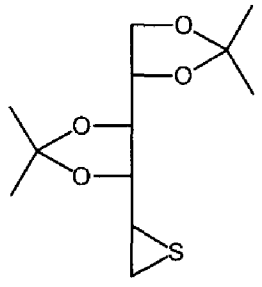
The reaction of oxiranes with thiourea is mechanistically analogous [3] to the reaction with thiocyanate ions (Scheme 8.2).



Scheme 8.2: Proposed mechanism for the synthesis of thiiranes via oxiranes using thiourea

The International Union of Pure and Applied Chemistry (IUPAC) recommends the name thiirane for a three-membered ring comprising one sulfur atom. When the more complex carbohydrate-based derivatives are considered the term "epithio" attached to the name of the sulfur-free skeleton seems to be a more convenient and acceptable system of nomenclature.[3]

Epithio sugars fall into two main categories - (a) those in which the sulfur ring comprises part of an open-chain system, such as with alditol derivatives or the exocyclic portion of a hexofurano compound, e.g. compounds **1** and **2**; or (b) where the sulfur ring forms part of a bicyclic system, e.g. compounds **3** and **4**, in which it is fused to a pyrano or furano structure, respectively. Several epithio sugar derivatives have been obtained from the reaction of oxiranes with thiocyanate ions or thiourea. Difficulties are sometimes experienced with these reactions. Treatment of compound **5** with thiourea yielded the episulfide **6** (63%) together with 20% of the elimination product **7**.[8] Presumably, a non-favoured conformational change from a chair to a boat intermediate would be required for the formation of **6** by the normal mechanism, which could account for the co-formation of the unsaturated compound. Nucleophilic attack by thioacetate ions on an oxirane followed by formation of an activated sulfonate ester of the hydroxyl group thereby generated, and subsequent treatment with base is an alternative route to episulfides. Creighton and Owen,[9] for example, obtained compounds **1** and **2** using this approach.



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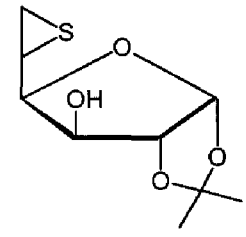

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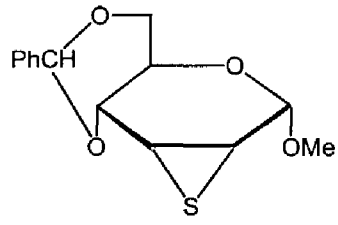

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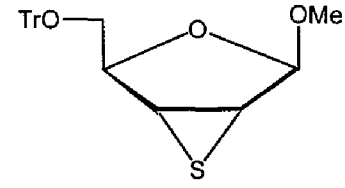

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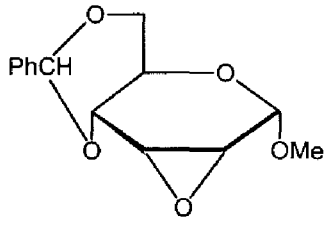

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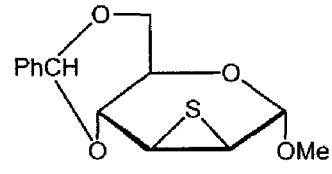

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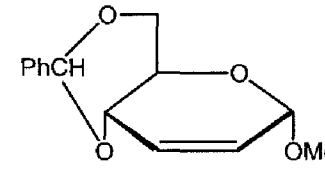

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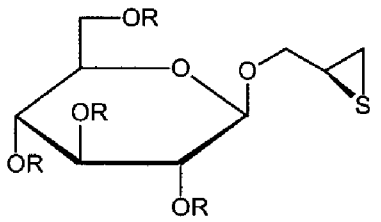
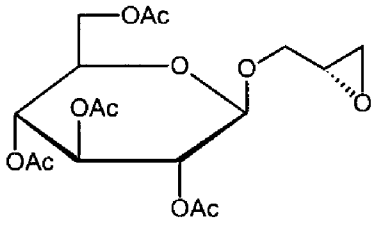
There is almost no information regarding sugar derivatives in which the thiirane ring is situated in the aglycon portion of a glycoside (epithioalkyl glycosides). These compounds could be of interest as glycolytic enzyme inhibitors. There is currently much interest in the synthesis and medicinal application of these types of compounds with main emphasis being placed on azasugars.[10] In only one study the synthesis of the epithiopropyl glucoside **8** and its tetra-acetate **9** *via* reaction of the oxirane **10** with thiourea has been described.[11]



8 R = H
9 R = Ac

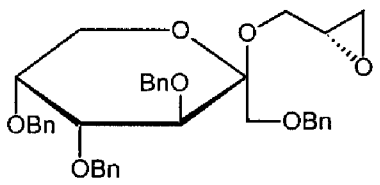


10

In keeping with the general explorative nature of the work described in this thesis, it was decided to investigate the synthesis of some epithioalkyl derivatives of D-fructose using generally established procedures.

8.2 Results and discussion

In chapter 5 it was demonstrated that the oxirane **11** is readily available from the diol **12** using two conventional routes. Treatment of compound **11** with potassium thiocyanate in aqueous ethanol or 1,4-dioxane gave the episulfide **13** in moderate yields of 52% and 58%, respectively. When the reaction was performed with thiourea in methanolic solution [12] at 50°C the yield of **13** was increased to 90%. Compound **13** was obtained as an oil.



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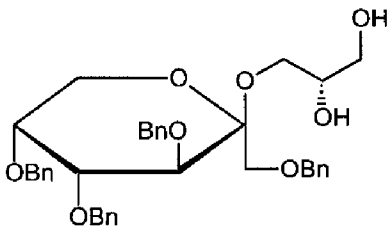

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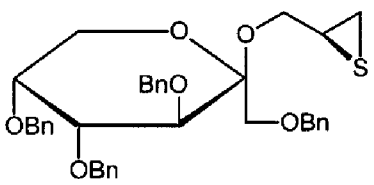


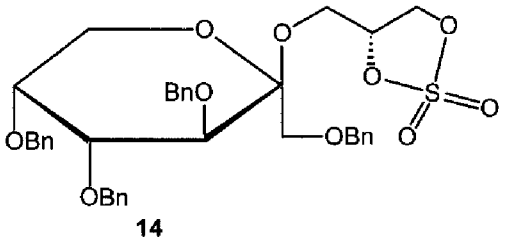
13

An alternative approach to obtain **13** was then investigated. It is known [13] that cyclic sulfates, which are readily obtainable from the corresponding vicinal diols, can function as oxirane equivalents in nucleophilic reactions. They are sometimes more reactive in this respect. They have not been widely used for the synthesis of thiiranes. Recent studies [14,15] have shown them to be useful activated intermediates for the synthesis of a wide variety of carbohydrate-based thiiranes, but no epiothioalkyl glycosides were reported.

Reaction of the cyclic sulfate **14** (see Chapter 5 for preparative details) in anhydrous acetone with potassium thiocyanate yielded the intermediate salt **15** in high yield (89%). Treatment of **15** with a solution of sodium methoxide in methanol gave the episulfide **13** in 51% yield.

A similar treatment of the cyclic sulfate **14** with potassium thioacetate afforded the S-acetyl intermediate **16** (84%), which on further reaction with methanolic sodium methoxide yielded compound **13** in 63.5% yield.

There appears to be little to choose between the two routes described for obtaining compound **13**. Although the yield from the oxirane **11** using thiourea in methanol solution was good (90%), the starting material may be considered less readily accessible than the cyclic sulfate **14**.



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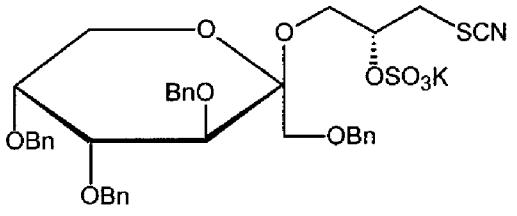

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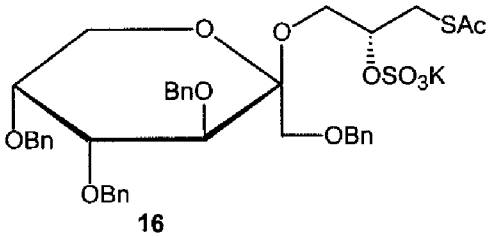

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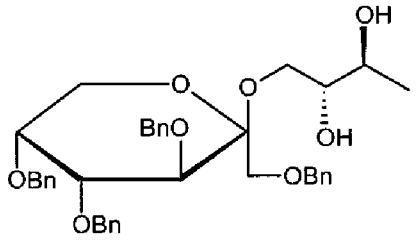
It was then decided to investigate the conversion of the dihydroxybutyl derivative **17** into the thiirane **21** using the cyclic sulfate **18** as an intermediate. Nucleophilic ring-opening of **18** with thiocyanate ions was not as straightforward as expected. The reaction was found to be



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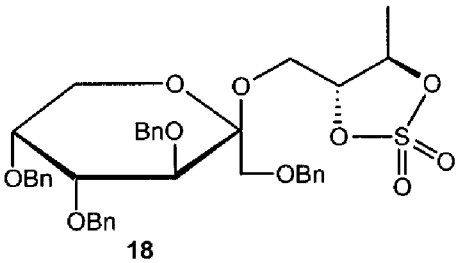

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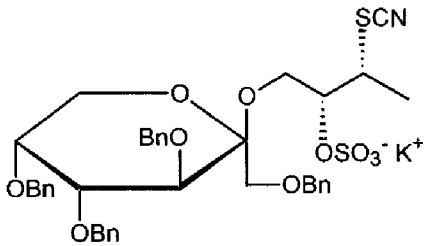

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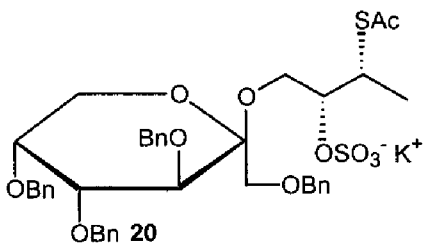

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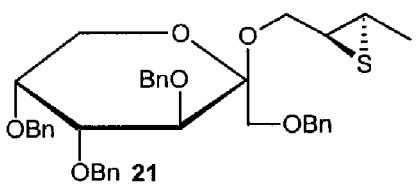

21

rather slow at normal temperature and analysis (TLC) indicated the presence of starting compound **18** even after 4 days. When the reaction was conducted at 60°C the expected salt **19** (63%) was obtained after 6 hr. Treatment of **19** with sodium methoxide gave the crystalline episulfide **21** in 49.5% yield. Compound **21** was obtained in much better yield by reaction of **18** with potassium thioacetate in acetone, followed by treatment of the resultant salt **20** (93.5%) with sodium methoxide in methanol to give **21** (81%).

Attempts were then made to remove the benzyl ether protecting groups from the episulfides **13** and **21**. Only partial debenzylation was observed when compounds **13** and **21** were subjected to catalytic hydrogenolysis over palladized charcoal (10%).[16] Analysis (TLC) indicated a complex mixture of products, including unreacted starting materials. Attempts to separate these mixtures by column chromatography were unsuccessful. Renewal of catalyst, increased reaction times, or higher pressures did not lead to satisfactory cleavage. These results were not unexpected and were probably due to the poisoning effects of sulfur on the catalyst. Debenzylation using sodium metal dissolved in liquid ammonia also led to unsatisfactory results. Complex mixtures were formed which could not be separated. Although this procedure [16,17] is useful when the substrate is contaminated or contains groups that could act as poison to hydrogenation catalysts, the sensitivity of the episulfide ring to various nucleophililes, especially amines, is well known.[1-4]

8.3 Concluding remarks

It may be concluded that although the formation of the first known epithioalkyl glycosides of D-fructose *via* dihydroxyalkyl derivatives was reasonably successful, careful choice of *O*-protecting functions is required. Benzyl ethers are not suitable in this respect because of difficulties encountered in their removal. Alternative methods available for cleavage include oxidation,[18] halogenation-hydrolysis,[19] and acetolysis.[20] These methods, however, suffer from serious defects of reagent incompatibility with the episulfide ring or glycosidic linkages. The original choice of benzyl ether protecting groups for diols **12** and **17** was made on the basis of best suitability in the asymmetric dihydroxylation reactions required for their formation. If the parent epithioalkyl β-D-fructopyranosides should be required for enzymes-inhibition studies then alternative blocking group strategies would need to be developed.

8.4 Experimental section

For general experimental procedures see Chapter 3.

2(S),3-Epithiopropyl 1',3',4',5'-tetra-O-benzyl-β-D-fructopyranoside (13)

Method A [21] **(*via* oxirane 11 with thiourea)**

A stirred solution of **11** (550 mg, 0.922 mmol) and thiourea (140 mg, 1.845 mmol, 2.0 eq) in methanol (10 mL) was heated at 50°C for 12 hr. The solution was then cooled, filtered, and concentrated *in vacuo*. The residue obtained was dissolved in dichloromethane (50 mL),

washed with water (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The oil was purified by column chromatography (n-hexane-ethyl acetate, 2:1) to give compound **13** (507.2 mg, 89.7%). $[\alpha]_D$ –62.0° ($CHCl_3$); ^{13}C-NMR ($CDCl_3$, 300 MHz) δ 138.78, 138.67, 138.53, 137.93, 128.29, 128.26, 128.19, 128.15, 127.77, 127.75, 127.64, 127.51, 127.40 (aromatic-C), 101.65 (C-2), 78.79 (C-3), 76.32 (C-4), 75.62 (benzylic-C), 73.66 (C-5), 73.56, 72.27, 71.24 (benzylic-C), 70.42 (C-1'), 66.61 (C-1), 61.33 (C-6), 33.01 (C-2') and 23.72(C-3') ppm. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.40-7.22 (m, 20H, aromatic H), 4.92, 4.65 (2d, 2H, J = 11.2 Hz, benzylic-H), 4.76, 4.71 (2d, 2H, J = 12.6 Hz, benzylic-H), 4.63, 4.42 (2d, 2H, J = 11.9 Hz, benzylic-H), 4.34 (d, 1H, J = 10.1 Hz, H-3), 4.06, 4.03 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.1 Hz, H-4), 3.85-3.82 (m, 2H, H-5, H-6), 3.74 (d, 1H, J = -10.1 Hz, H-1a), 3.60 (d, 1H, J = -10.1 Hz, H-1b), 3.51 (dd, 1H, J = 7.2 Hz, H-1'), 3.12 (m, 1H, H-2'), 2.48 (d, 1H, $J_{3'a,2'}$ = 6.0 Hz, H-3'a), 2.16 (d, 1H, $J_{3'b,2'}$ = 5.4 Hz, H-3'b) ppm.

Method B [9] **(*via* oxirane 11 with thiocyanate ions)**

A stirred mixture of compound **11** (350 mg, 0.586 mmol) and potassium thiocyanate (56.84 mg, 0.586 mmol, 1.0 eq) in 1,4-dioxane (10 mL) was heated at 50°C for 12 hr. The cooled reaction mixture was concentrated *in vacuo*, the residue was dissolved in dichloromethane (20 mL), washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (n-hexane-ethyl acetate, 2:1) of the crude residue gave **13** (208 mg, 58%). $[\alpha]_D$ –62.0° ($CHCl_3$).

In another experiment a stirred solution of compound **11** (220 mg, 0.368 mmol) in aqueous ethanol (10 mL) was treated with potassium thiocyanate (36 mg, 0.368 mmol, 1.0 eq) and set aside at room temperature. The reaction mixture was stirred at room temperature for 48 hr. The residue obtained after concentration *in vacuo* was dissolved in ether (20 mL), washed with saturated aqueous sodium chloride (2x10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (n-hexane-ethyl acetate, 2:1) of the residue gave **13** (118 mg, 52%). $[\alpha]_D$ –62.0° ($CHCl_3$).

Method C [15] **(*via* cyclic sulfate 14 with thiocyanate ions)**

*(2**R**)-O-Sulfo-3-S-cyano-3-thiopropyl 1',3',4',5'-tetra-O-benzyl* β-**D**-*fructopyranoside, potassium salt (15)*

A stirred solution of the cyclic sulfate **14** (443 mg, 0.655 mmol) in dry acetone was treated with potassium thiocyanate (70.67 mg, 0.720 mmol, 1.1 eq), and set aside at room temperature for *ca* 12 hr. The solution was then concentrated *in vacuo*, and the crude material purified by column chromatography (CH_2Cl_2-CH_3OH, 9:1) to give compound **15** as waxy material (452.7 mg, 89.3%). $[\alpha]_D$ –52.5° ($CHCl_3$); MS (FAB-Na^+) M/z, 796 (M^++ Na^+), 812 (M^++ K^+), ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 138.53, 138.44, 138.15, 137.57, 128.28, 128.25, 128.18, 128.13, 128.03, 127.96, 127.72, 127.66, 127.59, 127.47, 127.42, 127.31, 127.24 (aromatic-C), 113.59 (SCN), 101.43 (C-2), 78.56 (C-3), 76.22 (C-4), 75.41 (benzylic-C), 73.66 (C-5), 73.47, 71.87, 71.31 (benzylic-C), 70.05, 61.50, 61.36 (C-1, C-1', C-6), and 34.52 (C-3') ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.35-7.19 (m, 20H, aromatic H), 4.85 (d, 1H, J = 11.0 Hz, benzylic-H), 4.61-4.52 (m, 6H, benzylic-H), 4.29 (d, 1H, J = 11.8 Hz, benzylic-H), 4.23 (d, 1H, J = 10.0 Hz, H-3), 3.91, 3.88 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 2.87 Hz, H-4), 3.81-3.46 (m, 8H, H-1, H-1', H-2', H-5, H-6), 3.33, 3.30 (dd, 1H, H-3'a), 3.19, 3.15 (dd, 1H, H-3'b) ppm.

Method D [15] **(*via* cyclic sulfate 14 with thioacetate ions)**

*2(**R**)-O-Sulfo-3-S-acetyl-3-thiopropyl 1',3',4',5'-tetra-O-benzyl β-D-fructopyranoside, potassium salt (**16**)*

A stirred solution of the cyclic sulfate **14** (930 mg, 1.375 mmol) in dry acetone was treated with potassium thioacetate (172.79 mg, 1.513 mmol, 1.1 eq), and set aside at room temperature for 3 hr. The mixture was concentrated *in vacuo*, and the crude material purified by column chromatography (CH_2Cl_2-CH_3OH, 9:1) to give compound **16** as waxy material (906 mg, 83.4%). $[\alpha]_D$ –38.6° ($CHCl_3$); MS (FAB-Na^+) M/z, 813 (M^++ Na^+), 829 (M^++ K^+), ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 195.97 (*C*=O), 138.64, 138.48, 138.00, 137.62, 128.83, 128.60, 128.47, 128.28, 128.23, 128.21, 128.12, 128.03, 127.90, 127.72, 127.57, 127.45, 127.38, 127.27, 127.16(aromatic-C), 101.23 (C-2), 78.72 (C-3), 76.41 (C-4), 76.14, 75.38 (benzylic-C), 73.50 (C-5), 73.43, 71.92 (benzylic-C), 71.30 (C-1'), 70.08 (C-2'), 66.61 (C-1), 61.38 (C-6), 30.44 (OCH_3) and 29.26 (C-3') ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.35-7.19 (m, 20H, aromatic H), 4.86 (d, 1H, J = 10.9 Hz, benzylic-H), 4.67-4.53 (m, 6H, benzylic-H), 4.30 (d, 1H, J = 11.8 Hz, benzylic-H), 4.23 (d, 1H, J = 10.1 Hz, H-3), 3.99, 3.96 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 2.9 Hz, H-4), 3.78-3.37 (m, 8H, H-1, H-1', H-2', H-5, H-6), 3.10, 3.05 (dd, 1H, H-3'), 2.19 (OCH_3) ppm.

A stirred solution of compound **15** (230 mg, 0.297 mmol) in anhydrous methanol (10mL) was treated with a solution of sodium methoxide (1M), and set aside at room temperature until the TLC showed complete disappearance of the starting material. The reaction mixture was then concentrated *in vacuo*, treated with water (10 mL) and the resulting solution extracted with ethyl acetate (2x20 mL). The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (n-hexane-ethyl acetate, 2:1) to give **13** as an oil (92 mg, 50.61%). $[\alpha]_D$ –62.2° ($CHCl_3$).

A stirred solution of compound **16** (825 mg, 1.044 mmol) in anhydrous methanol (10 mL) was treated with a solution of sodium methoxide (1M) in the same manner as described above to give **13** (406 mg, 63.5%). $[\alpha]_D$ –62.1° ($CHCl_3$).

*2(**R**)-O-Sulfo-3-S-cyano-3-S-thiobutyl-1',3',4',5'-tetra-O-benzyl-β-D-fructopyranoside, potassium salt (**19**).*

A stirred solution of compound **18** (220 mg, 0.318 mmol) in dry acetone (20 mL) was treated with potassium thiocyanate (33.93 mg, 0.349 mmol, 1.1 eq) and heated at 60°C for 6 hr. The cooled solution was concentrated *in vacuo*, and the crude material purified by column chromatography (CH_2Cl_2-CH_3OH, 9:1) to give **19** as waxy material (158 mg, 63%). $[\alpha]_D$ –26.7° ($CHCl_3$); MS (FAB-Na^+) M/z 810 (M^++ Na^+), 826 (M^++ K^+), ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 138.41, 138.32, 137.66, 137.21, 128.65, 128.54, 128.42, 128.34, 128.30, 128.22, 127.98, 127.85, 127.77, 127.66, 127.56, 127.53, 127.31 (aromatic-C), 112.35 (SCN), 101.14 (C-2), 78.52 (C-3), 76.43 (C-4), 75.43 (benzylic-C), 73.51 (C-5), 73.27, 71.90, 71.48 (benzylic-C), 70.02, 61.61, 60.07 (C-1, C-1', C-6), 45.50 (C-3'), and 17.54 (CH_3) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.35-7.19 (m, 20H, aromatic H), 4.88 (d, 1H, J = 11.0 Hz, benzylic-H), 4.66-4.54 (m, 6H, benzylic-H), 4.27 (d, 1H, J = 11.7 Hz, benzylic-H), 4.20 (d, 1H, J = 10.0 Hz, H-3), 3.97, 3.93 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 2.82 Hz, H-4), 3.85-3.71 (m, 8H, H-1, H-1', H-2', H-5, H-6), 3.34, 3.30 (d, 1H, J = 10.3 Hz, H-3'), 1.42 (d, 3H, CH_3) ppm.

*2(***R***)-O-Sulfo-3-*S*-acetyl-3-*S*-thiobutyl 1',3',4',5'-tetra-O-benzyl* β-D-*fructopyranoside, potassium salt (20).*

A stirred solution of the cyclic sulfate **18** (609 mg, 0.882 mmol) in dry acetone (10 mL) was treated with potassium thioacetate (110.80 mg, 0.970 mmol, 1.1 eq) and set aside at room temperature for 2 hr. The mixture was concentrated *in vacuo*, and the crude material purified by column chromatography (CH_2Cl_2-CH_3OH, 9:1) to give compound **20** as waxy material (663 mg, 93.5%). $[\alpha]_D$ –38.6° ($CHCl_3$); MS (FAB-Na^+) M/z 827 (M^++ Na^+), 843 (M^++ K^+), ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 195.72 (*C*=O), 138.60, 138.38, 137.55, 137.32, 128.64, 128.37, 128.30, 128.25, 128.04, 127.93, 127.85, 127.76, 127.65, 127.53, 127.46 (aromatic-C), 101.19 (C-2), 78.69 (C-3), 76.79 (C-4), 76.56, 75.53 (benzylic-C), 73.59 (C-5), 73.48, 72.24 (benzylic-C), 71.48 (C-1'), 70.18 (C-2'), 61.73 (C-1), 60.90 (C-6), 40.39 (C-3'), 30.63 (O*C*H_3) and 17.66 (*C*H_3) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.37-7.21 (m, 20H, aromatic H), 4.87 (d, 1H, J = 10.7 Hz, benzylic-H), 4.70-4.54 (m, 6H, benzylic-H), 4.29 (d, 1H, J = 11.8 Hz, benzylic-H), 4.19 (d, 1H, J = 10.1 Hz, H-3), 4.10 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 2.8 Hz, H-4), 3.98 (m, 1H, H-5), 3.89-3.54 (m, 7H, H-1, H-1', H-2', H-6), 3.42 (d, 1H, J = 10.39 Hz, H-3'), 2.19 (OC*H*$_3$), 1.29 (d, 3H, J = 7.2 Hz, C*H*$_3$) ppm.

*2(***S***),3(***S***)-Epithiobutyl 1',3',4',5'-tetra-O-benzyl* β-D-*fructopyranoside (21).*

A stirred solution of compound **20** (250 mg, 0.310 mmol) in anhydrous methanol (10 mL) was treated with 1**M** solution of sodium methoxide in methanol and set aside at room temperature until TLC showed complete disappearance of the starting material. The reaction mixture was concentrated *in vacuo*, treated with water (10 mL), and the resulting solution was extracted with ethyl acetate (2x20 mL). The combined organic layer was dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (n-hexane-ethyl acetate, 2:1) to give compound **21** (158 mg, 81.17%). A sample of the product was crystallized (ether / ethanol) to give pure **21**. m.p. 179 C; $[\alpha]_D$ –62.2° ($CHCl_3$); MS (FAB-Na^+) M/z 849 (M^++ Na^+), 865 (M^++ K^+), ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 138.82, 138.62, 138.50, 137.90, 128.40, 128.24, 128.08, 128.03, 127.85, 127.77, 127.74, 127.70, 127.64, 127.61, 127.47, 127.42, 127.32 (aromatic-C), 101.62 (C-2), 78.64 (C-3), 76.24 (C-4), 75.76 (benzylic-C), 73.60 (C-5), 73.52, 72.18, 71.16 (benzylic-C), 70.36 (C-1'), 65.96 (C-1), 61.26 (C-6), 41.95 (C-2'), 36.26 (C-3'), and 21.28 (*C*H_3) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.40-7.22 (m, 20H, aromatic H), 4.93 (d, 1H, J = 11.2 Hz, benzylic-H), 4.76, 4.71 (2d, 2H, J = 12.6 Hz, benzylic-H), 4.69-4.60 (m, 3H, benzylic-H), 4.42 (d, 1H, J = 11.8 Hz, benzylic-H), 4.38 (d, 1H, J = 10.1 Hz, H-3), 4.05, 4.01 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 3.0 Hz, H-4), 3.90-3.68 (m, 5H, H-1', H-1, H-5, H-6), 3.58 (d, 1H, J = -10.1 Hz, H-1), 3.49, 3.45 (dd, 1H, J = 7.1 Hz, H-1'), 2.88-2.82 (m, 1H, H-2'), 2.48 (d, 1H, $J_{3'a,2'}$ = 5.61 Hz, H-3'), 1.46 (d, 3H, J = 5.7 Hz, C*H*$_3$) ppm. *Anal* calc for $C_{39}H_{42}O_6S$: C 72.82; H 6.75; S 5.12. Found: C 72.36; H 7.01; S 5.14%.

Compound **19** (158 mg, 0.200 mmol) was converted by the same procedure described above to give **21** (62.7mg, 49.52%). m.p. 179°C; $[\alpha]_D$ –62.2° ($CHCl_3$).

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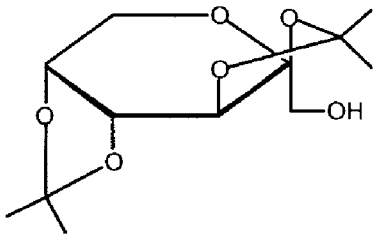
CHAPTER 9

SYNTHESIS OF A GLYCERYL-ETHER AND SOME RELATED COMPOUNDS FROM 2,3:4,5-DI-*O*-ISOPROPYLIDENE-β-D-FRUCTOPYRANOSE

9.1 Introduction

Iodine-catalyzed acetalation has been used [1a] successfully in the direct synthesis of specific isopropylidene acetals of D-fructose. The employment of iodine in other areas of carbohydrate chemistry has been reviewed.[1b]

The mechanism of the iodine catalyzed-acetalation reaction involves two steps, which include the formation of an acetone-iodine complex followed by partial or complete acetalation of vicinal diol groups.[1] Depending on the reaction conditions, acetalation of D-fructose can furnish compounds **1** or **2**. Diacetal **1** is obtained [1] when D-fructose is treated with catalytic amount of iodine in boiling acetone. Compound **2** is formed when the reaction is performed at room temperature. These results indicate that compound **1** is the thermodynamically-controlled product, whereas compound **2** results from kinetic control reaction. Compound **2** has been employed as an intermediate in the synthesis of other fructosyl derivatives, and also some new non ionic-surfactants.[1,2] The use of other reaction conditions and catalysts do not result in the above specificity and the product mixtures needs to be separated by fractional crystallization.[3]



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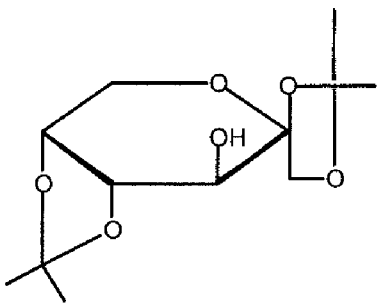

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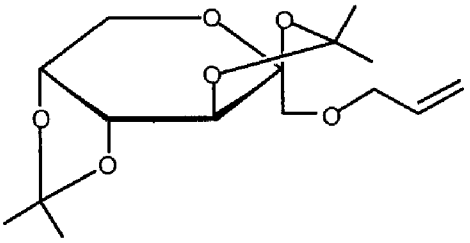
It was of interest to investigate the applicability of some of the reaction procedures employed in the earlier chapters on compound **1**. The contents of this chapter report on the preliminary results of the syntheses of some derivatives of 1-*O*-glyceryl β-D-fructopyranose starting from 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose (**1**). It is possible that some of them could be interesting artificial sweetening agents since both D-fructose and glycerol are quite sweet themselves.[4] The 1-*O*-ether linkage may make these compounds less susceptible to enzymic cleavage and could be of interest as non-calorigenic materials. Many biological tests and screening programmes would be required before they could be accepted for this purpose.

9.2 Results and discussion

Compound **1** (59%) was obtained by treatment of D-fructose in acetone in the presence of a catalytic amount of iodine (0.05 eq) as described.[1] A solution of compound **1** in dimethyl sulfoxide was treated with allyl bromide in the presence of powdered potassium hydroxide to give the 1-*O*-allyl ether **3** (92%). Compound **3** has been described previously [5,6] and resulted from treatment of **1** in anhydrous tetrahydrofuran (THF) with allyl bromide in the presence of sodium hydride. The procedure described here was considered more convenient in terms of the reagents used and the processing of the product mixture.

Dihydroxylation of compound **3** was carried out using potassium permanganate or potassium (VI) osmate as oxidizing agents. Treatment of compound **3** in a mixture of acetone / water with potassium permanganate gave a racemic mixture of the diols **4** (93%). Alternatively, compound **4** was obtained by an asymmetric dihydroxylation reaction (Sharpless type) performed using $(DHQD)_2PHAL$ as a chiral ligand. Treatment of compound **3** with potassium osmate (VI) dihydrate and $K_3[Fe(CN)_6]$ in the presence of the chiral ligand $(DHQD)_2PHAL$ afforded compound **4** (99.8%). The stereoselectivity of the oxidation reactions could not be determined by GLC analysis since the acetyl derivatives obtained by acetylation of the hydroxyl groups of the aglycon moiety of **4** were not separated. The optical rotation of the product (-23°) compared with that (-25.5°) obtained by permanganate oxidation indicated little or no stereoselectivity.



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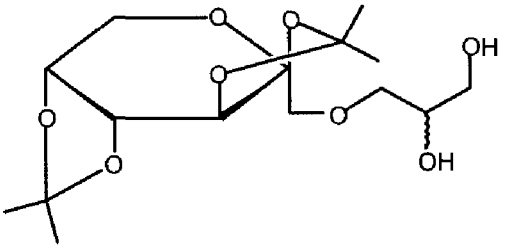

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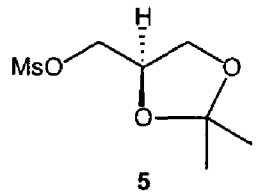
Attempts were also made to obtain alternative derivatives of the diol **4** by coupling reactions of **1** with some isopropylidene glycerol derivatives. Treatment of compound **1** with (4*R*)-methanesulfonate derivative **5** [7] under basic conditions furnished compound **8** (56.3%) with defined stereochemistry at C-2 of the glycerol unit. Reaction of **1** with the racemic monotosylate **6** [8] in the same manner gave an inseparable mixture of unreacted **6** and compound **9** (GLC: **6**: 17%, **9**: 81%). Attempts to obtain compound **9** by treatment of compound **1** with the chloro derivative **7** were not successful, compound **7** appeared to be rather unreactive under the reaction conditions. Attempts to selectively remove the exoclyclic isopropylidene groups from compounds **8** and **9** were not wholly successful. Reaction of both derivatives with dilute aqueous acetic acid (50-80%) gave complex mixtures (TLC) of compounds, including some free glycerol, which indicated that some glycosidic hydrolysis had occurred. The reaction conditions employed do not normally cause this type of hydrolysis and cyclic isopropylidene groups forming parts of biyclic systems usually remain intact.[9]



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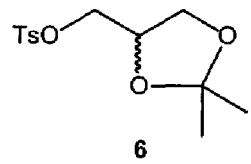

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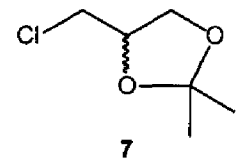

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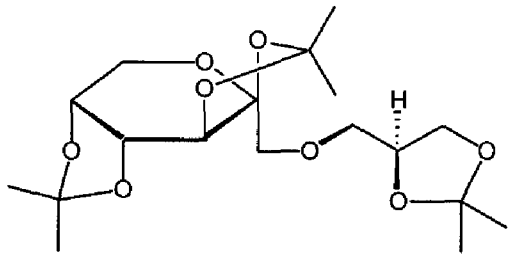

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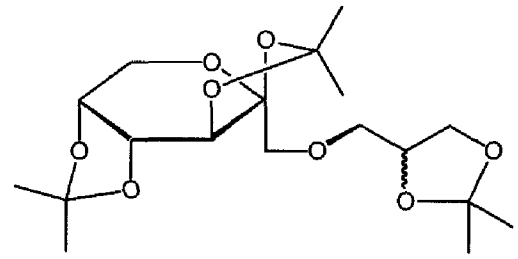
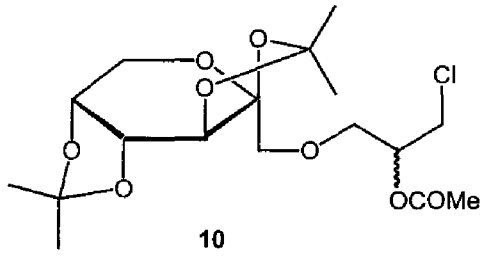


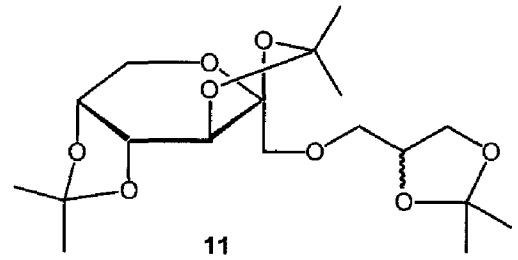
9

Subsequent conversion of racemic compound **4** into the oxirane **12** was then achieved by employing a synthetic procedure which involved the intermediate formation of the halohydrin ester **10** (see Chapter 5 for details). Treatment of a solution of **4** in dichloromethane with triethylorthoacetate and trimethylsilyl chloride at 0°C gave **5** which was transformed into the oxirane **12** (39%) using sodium methoxide. The yield of the product was improved when the reaction was carried out in the presence of potassium carbonate. Treatment of a solution of **10** in methanol with potassium carbonate gave the oxirane **12** (76%).

Ring opening of the oxirane **12** with azide ions gave azido alcohols **13**, as intermediates for the syntheses of amino alcohols **14,** and thence the aziridine derivative **19**. The ring opening of oxirane **7** was accomplished by treatment with sodium azide in the presence of ammonium sulfate. This reaction generated a mixture of two regioisomers **13** (89%) in a ratio of 2:1 (^{1}H, and ^{13}C-NMR) which could not be separated. Reaction of compound **4** with dimethyl carbonate in the presence of DBU at 60°C gave the corresponding cyclic carbonate derivative **11** (87%). Treatment of compound **11** in *N,N*-dimethylformamide with sodium azide at 80°C for five days afforded compounds **13** (32%). Once again this low yield does not support the earlier results [10] which suggested that cyclic carbonate esters can be useful activated intermediates for the intro-



10



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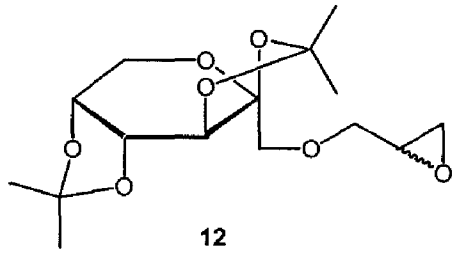
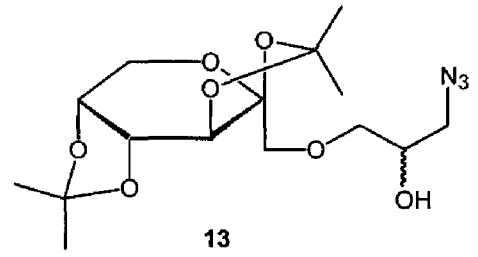


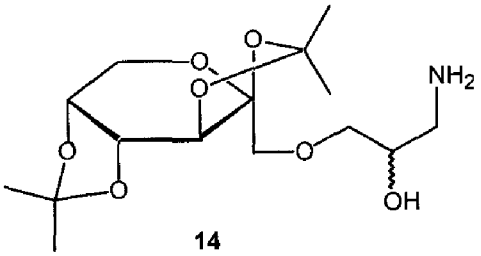
12



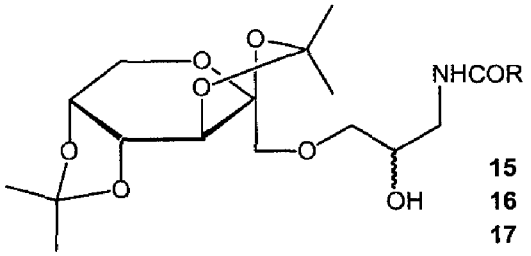
13

duction of substituents on carbon using nucleophilic attack. The site of main attack must be on the electron-deficient carbonyl carbon, leading to decarbonylation.[10]

Reduction of the azido alcohols **13** to obtain amino alcohols **14** was carried out using two procedures. The first approach involved reduction of **13** with lithium aluminium hydride in ether at room temperature to yield **14** (69%). The second route involved treatment of the mixed alcohols in pyridine with triphenylphosphine [12] until evolution of nitrogen ceased. This type of reaction gives initially an imino-phosphirane, then an oxazaphosphine intermediate, which can be converted to amino alcohols. The corresponding amino alcohols **14** were obtained by hydrolysis of this inter-mediate with (25%) aqueous ammonia solution.[13] The yield (75%) of the amino alcohols **14** from this reaction was only slightly higher than that obtained using the other reduction method (69%).



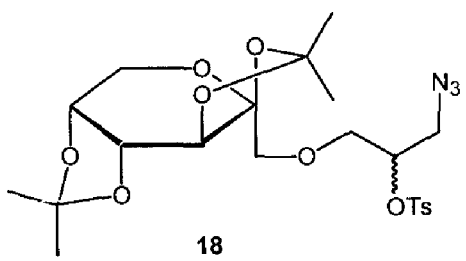
14



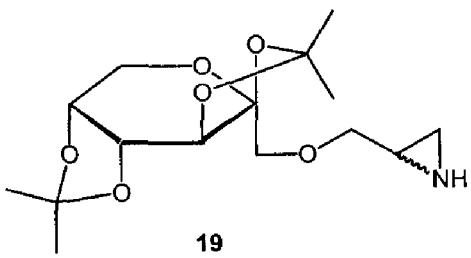
15 R = $C_{11}H_{23}$
16 R = $C_{13}H_{27}$
17 R = $C_{15}H_{31}$

Attention was then directed towards the synthesis of the mono-amide derivatives **15**, **16**, and **17** from amino alcohols **14**. For this purpose three fatty acid chlorides were selected *viz*, lauroyl, myristic and palmitoyl. Selective acylation reaction of **14** with these fatty acid chlorides at 0°C furnished the mono amide derivatives **15** (82%), **16** (81%), and **17** (62%), after 30 minutes.

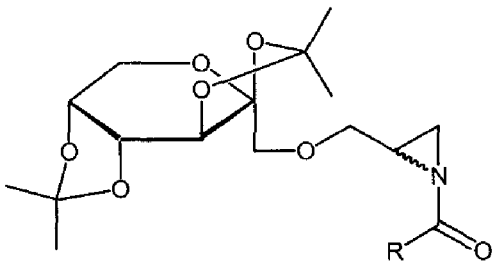
Transformation of azido alcohols **13** into the aziridine derivative **19** was carried out *via* the monosulfonate derivatives **18**. Treatment of **13** with *p*-toluenesulfonyl chloride in pyridine gave the corresponding monosulfonate derivatives **18** (84%). Reduction of **18** using lithium aluminium hydride caused concomitant cyclization to give the racemic aziridine derivative **19** (62%). The product obtained from this reaction was transformed into *N*-acyl aziridine derivatives using the above fatty acid chlorides. Treatment of compound **19** in dichloromethane with the fatty acid chloride at -18°C under basic conditions (triethylamine) furnished the *N*-acyl aziridine derivatives **20** (85%), **21** (74%), and **22** (88%), respectively.



18



19



20 R = $C_{11}H_{23}$
21 R = $C_{13}H_{27}$
22 R = $C_{15}H_{31}$

9.3 Concluding remarks

The preliminary results described in this chapter show that long-chain mono acyl amino and *N*-acyl aziridine derivatives can be obtained fairly readily from the intermediates **14** and **19** in moderately good yields. Conversion of the diol **4** into the terminal azide **13** was achieved via nucleophilic attack by azide ions on the oxirane **12**. Attempts to selectively remove the exocyclic isopropylidene groups from compounds **8** and **9** by hydrolysis (dilute aqueous acetic acid) were unsuccessful. Reduction of the azido alcohols **13** to obtain compound **14** was carried out using two procedures. Treatment of the monosulfonate derivative **18** with lithium aluminium hydride ($LiAlH_4$) gave the racemic aziridine derivative **19**.

9.4 Experimental section

For general experimental procedures see Chapter 3.

1-O-allyl-2,3:4,5-di-O-isopropylidene-β-D-fructopyranose (3)

A stirred mixture of compound **1** (5.0385 g, 19.35 mmol) in dimethyl sulfoxide (20 mL) containing powdered potassium hydroxide (1.629 g, 29.0 mmol, 1.5 eq) was treated with allyl bromide (2.52 mL, 29.0 mmol, 1.5 eq). The mixture was stirred at room temperature for *ca* 12 hr and then treated with ether (100 mL) and water (40 mL). The separated aqueous layer was extracted with more ether (50 mL), and the combined organic layers were washed with saturated sodium chloride (3x20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Column chromatography (n-hexane-ethyl acetate, 3:1) of the crude material gave compound **3** (5.3167 g, 92%) as a pure colourless oil; $[\alpha]_D$ –32.9° ($CHCl_3$) ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 134.60, 116.76, 106.94, 106.50, 102.79, 76.47, 75.93, 72.77, 71.45, 71.12, 70.31, 70.14, 61.07, 26.62, 25.92, 25.39, and 24.12 ppm. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 6.10-5.72 (m, 1H, -OCH_2CH=CH_2), 5.45-5.07 (m, 2H, -OCH_2CH=CH_2), 4.60 (dd, 1H, $J_{4,3}$ = 2.6 Hz, $J_{4,5}$ = 8.9 Hz H-4), 4.21 (d, 1H, $J_{3,4}$ = 2.6 Hz), 4.35-3.98 (m, 3H), 3.97-3.62 (m, 2H), 1.54, 1.47, 1.44, 1.35(4s, each 3H, CMe_2) ppm.

1-O-(2',3'-Dihydroxypropyl)-2,3:4,5-di-O-isopropylidene-β-D-fructopyranose (4)

Method (a) using $K_2OsO_2(OH)_4$ and $(DHQD)_2$.PHAL:

A cooled (0°C) mixture of $(DHQD)_2$.PHAL (8.0 mg), $K_2OsO_2(OH)_4$ (1.6 mg), K_2CO_3 (415 mg), and $K_3Fe(CN)_6$ (980 mg) in water (5 mL) was added to a stirred solution of **3** (508 mg, 1.0 mmol) in *t*-butyl alcohol (5 mL). The reaction mixture was stirred vigorously for 5 hr, quenched by addition of Na_2SO_3 (1.5 g) and stirred for a further 1 hr. The mixture was then treated with water (10 mL) and extracted with ether (3x15 mL). The combined organic layers were washed with saturated sodium chloride (10 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give **4** (535 mg, 98%) as a syrup; $[\alpha]_D$ – 25.0° ($CHCl_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 108.95, 108.54 [*C*-$(CH_3)_2$], 102.41 (C-2), 75.82, 73.43, 73.21 (C-1, C-1'), 70.79, 70.74, 70.63, 70.25 (C-3, C-4, C-5, C-2'), 63.64 (C-6), 63.54 (C-3'), 29.16, 26.38, 25.72, 25.69 (isopropylidene C) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 4.62-4.55 (m, 1H, H-4), 4.32 (d 1H, J = 2.9 Hz, H-3), 4.24(d, 1H, $J_{5,4}$ = 8.2 Hz, H-5), 3.95-3.75 (m, 2H, H-6), 3.80-3.40 (m, 7H, H-1, H-1', H-2', H-3'), 3.07 (d, 1 / 2H, J = 3.6 Hz, O*H*), 2.76 (d, 1 / 2H, J = 4.7 Hz, O*H*), 1.54, 1.50, 1.49, 1.41, 1.35(5s, each 3H, CMe_2) ppm.

Method (b) using potassium permanganate:

A solution of potassium permanganate (1.11 g, 7 mmol) in water (17 mL) was added dropwise to a stirred cooled (0°C) solution of **3** (2.0 g, 6.66 mmol) in acetone (33 mL) and water (25 mL). The reaction mixture was maintained at this temperature for 1 hr. The manganese dioxide that was formed was removed by filtration, washed successively with water (100 mL), acetone (50 mL), and ether (50 mL). The separated aqueous layer was extracted with ether (3x50 mL), and the combined organic layer washed with brine (100 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Column chromatography (n-hexane-ethyl acetate, 1:2) of the crude material gave **4** (2.10 g, 93%) as a syrup. $[\alpha]_D$ – 23.3° ($CHCl_3$).

*2,2-dimethyl-4(**R**)-methanesulfonyloxymethyl-1,3-dioxolane (5)*

A cooled (0°C), stirred solution of (*S*)-1,2-O-isopropylideneglycerol (1 g, 7.58 mmol) in pyridine (5 mL) was treated with mesyl chloride (1.04 g, 9.09 mmol, 1.2 eq) for 1 hr, and then set aside in the refrigerator (5°C) for 1 hr. The mixture was then treated with a mixture of ice / water (75 mL), stirred for 1 hr, and the aqueous layer extracted with dichloromethane (75 ml). The organic layer was washed, successively with aqueous hydrochloric acid (2N, 75 mL), water (75 mL) and a solution of saturated sodium hydrogen carbonate (75 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield compound **5** (1.56 g, 96.3 %) as a colourless oil. $[\alpha]_D$ –5.1° ($CHCl_3$); lit [7] $[\alpha]_D$ –7.4° ($CHCl_3$) ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 4.52-3.72 (m, 5H), 3.07 (s 3H, $-OSO_2CH_3$), 1.45, 1.37 (2s, each 3H, CMe_2) ppm.

rac *2,2-dimethyl-4-p-toluenesulfonyloxymethyl-1,3-dioxolane (6)*

A cooled (0°C), stirred solution of solketal (5 g, 37.9 mmol) in dry pyridine (10 mL) was treated with tosyl chloride (8.7 g, 45.5 mmol, 1.2 eq). The mixture was set aside at room temperature for 1 hr. and then treated with a mixture of ice / water (150 mL). After 2 hr. the aqueous layer was extracted with dichloromethane (75 ml), dried (Na_2SO_4) and concentrated *in vacuo*. Crystallization of the crude product from di-isopropyl ether / n-hexane yielded compound **6** (8.59 g, 79%). m.p. 47-49°C (Lit [14]: m.p. = 47°C). ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 7.81 (d, 2H, J = 8.3 Hz, benzylic-H), 7.36 (d, 2H, J = 8.3 Hz, benzylic-H), 4.45-4.13 (m, 1H), 4.13-3.68 (m, 1H), 2.46 (s 3H, $-OSO_2PhCH_3$), 1.34, 1.32 (2s, each 3H, CMe_2) ppm.

4-chloromethyl-2,2-dimethyl-1,3-dioxolane (7)

A stirred solution of 3-chloro-1,2-propanediol (1 g, 9.1 mmol) in acetone (10 mL) was treated with DMP (2 mL) and $TsOH.H_2O$ (10 mg), and set aside at room temperature until TLC showed complete disappearance of the starting material (30 minutes). The mixture was neutralized with K_2CO_3, filtered, and concentrated *in vacuo* to give an oil (1.23 g). Kógel ruhr distillation (70°C, 12mmHg) gave compound **7** (630 mg, 46%) as a colourless oil. ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 4.48-3.80 (m, 3H), 3.71-3.31 (m, 2H), 1.45, 1.37 (2s, each 3H, CMe_2) ppm.

*1-O-2(**R**',3'-isopropylidenedioxypropyl)-2,3:4,5-di-O-isopropylidene-β-**D**-fructopyranose (8)*

A stirred, cooled (15°C) mixture of compound **1** (850 mg, 3.27 mmol) in dimethyl sulfoxide (5 mL) containing potassium hydroxide (280 mg, 4.90 mmol, 1.5eq) was treated with compound **5** (1.03 g 4.90 mmol, 1.5 eq), and set aside at room temperature for 48 hr. The reaction mixture was diluted with ether (75 mL) and water (20 mL). The separated aqueous layer

was extracted with ether (40 mL) and the combined organic layers were washed with saturated sodium chloride (3x50 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Column chromatography (n-hexane-ethyl acetate, 1:1) of the crude material gave compound **8** (700 mg, 56.3%) as a colourless oil; $[\alpha]_D$ –17.2° (CH_2Cl_2); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 109.25, 108.92, 108.58 [*C*-$(CH_3)_2$], 102.54 (C-2), 76.68, 74.33 (C-1, C-1'), 70.98, 70.16, 69.99, 66.97 (C-2', C-3, C-4, C-5), 61.02 (C-6), 26.77, 26.54, 25.87, 25.30, 24.00 (isopropylidene C) ppm. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 4.59 (dd, 1H, $J_{3,4}$ = 2.6 Hz, $J_{5,4}$ = 7.9 Hz, H-4), 4.36 (d 1H, $J_{3,4}$ = 2.6 Hz, H-3), 4.26(m, 1H H-2'), 4.21 (dd, 1H, $J_{5,4}$ = 7.9 Hz, $J_{5,6}$ = 1.3 Hz, H-5), 4.04 (dd, 1H, $J_{1'a,1'b}$ = 6.4 Hz, $J_{1'a,2'}$ = 8.2 Hz, H-1a'), 3.90 (dd, 1H, $J_{6ax,6eq}$ = 12.9 Hz, $J_{6ax,5}$ = 1.9 Hz, H-6ax), 3.78 (dd, 1H, $J_{1'b,1'a}$ = 6.2 Hz, $J_{1'b,2'}$ = 8.2 Hz, H-1'b), 3.72(m, 1H, H-3'a), 3.71 (d, 1H, $J_{6ax,6eq}$ = 12.9 Hz, H-6eq), 3.62 (dd, 2H, $J_{1a,\,1b}$ = 10.8 Hz, $J_{1b,1a}$ = 12.2 Hz, H-1), 3.52 (dd, 1H, $J_{3'b,\,3'a}$ = 6.2 Hz, $J_{3'b,2'}$ = 10.1 Hz, H-3'b), 1.54, 1.47, 1.41, 1.36, 1.35, 1.34 (6s, each 3H, CMe_2) ppm.

1-O-(2'-Acetoxy-3'-chloropropyl)-2,3:4,5-di-O-isopropylidene-β-D-fructopyranose (10)

A stirred cooled (0°C) solution of the diol **4** (1.18 g, 3.53 mmol) in dichloromethane (10 mL) was treated with trimethylsilyl chloride (1.12 mL, 8.82 mmol, 2.5 eq) and triethyl *ortho*acetate (0.88 mL, 7.06 mmol, 2.0 eq). The mixture was stirred for 1 hr, concentrated *in vacuo* and the resultant material purified by column chromatography (n-hexane-ethyl acetate, 9:1) to yield compound **10** (1.167 g, 90.7 %) as a colourless oil; $[\alpha]_D$ –30.7° ($CHCl_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 169.99 (*C*=O), 108.86, 108.52 [*C*-$(CH_3)_2$], 102.27 (C-2), 72.92, 72.82 (C-1, C-1'), 70.86, 70.04, 69.94, 69.13 (C-2', C-3, C-4, C-5), 60.95 (C-6), 42.61 (C-3'), 26.45, 25.88, 25.20, 23.93 (isopropylidene C), and 21.82 (CO*C*H_3) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 4.60, 4.59 (dd, 1H, $J_{3,4}$ = 2.58 Hz, H-4), 4.35 (d 1H, J = 2.4 Hz, H-3), 4.23 (d, 1H, $J_{5,4}$ = 7.9 Hz, H-5), 3.93, 3.88 (dd, 1H, $J_{5,6ax}$ = 1.8 Hz, H-6ax), 3.84-3.46 (m, 7H, H-6eq, H-1, H-1' H-3'), 2.09 (s, 3H, CO*C*H_3), 1.53, 1.47, 1.40, 1.34 (4s, each 3H, CMe_2) ppm.

1-O-(2',3'-Oxiranylpropyl)-2,3:4,5-di-O-isopropylidene-β-D-fructopyranose (12)

Method (a): [13]

A solution of **10** (945.5 mg, 2.392 mmol) in methanol (5 mL) was treated with potassium carbonate (660 mg, 4.784 mmol, 2 eq) and the suspension was stirred vigorously at room temperature for 3 hr, filtered, and inorganic residue was washed with dichloromethane. The combined filtrate and washings were concentrated *in vacuo* and the resultant residue purified by column chromatography (n-hexane-ethyl acetate, 2:1) to give **12** (573 mg, 75.7%) as a colourless oil; $[\alpha]_D$ –35.3° ($CHCl_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 108.84, 108.51 [*C*-$(CH_3)_2$], 102.46 (C-2), 72.57, 72.29 (C-1, C-1'), 70.90, 70.09, 69.97 (C-3, C-4, C-5), 60.95(C-6), 50.61, 50.48 (C- C-2') 44.17, 44.08 (C-3'), 26.48, 25.85, 25.18, 23.95 (isopropylidene C) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 4.61, 4.59 (dd, 1H, $J_{3,4}$ = 2.58 Hz, 4), 4.39 (d, 1H, J = 2.62 Hz, 3), 4.23 (d, 1H, $J_{5,4}$ = 7.9 Hz, 5), 3.92, 3.88 (dd, 1H, $J_{5,6ax}$ = 1.8 Hz, 6ax), 3.76-3.59 (m, 4H, 6eq, 1, 1'), 3.16-3.14 (m, 1H, 2'), 3.46, 3.42 (dd, 1H, $J_{1',2'}$ = 6.06 Hz, 1'), 2.78 (dd, 1H, J = 4.6 Hz, 3'), 2.60, 2.59 (dd, 1H, J = 2.68 Hz, 3'), 1.54, 1.47, 1.40, 1.34 (4s, each 3H, CMe_2) ppm.

Method (b): [13]

A stirred, cooled (0°C) solution of **10** (920 mg, 2.329 mmol) in dichloromethane (10 mL) was treated with sodium methoxide 1M (1 mL) and then left at room temperature for 6 hr. The

mixture was diluted with dichloromethane (50 mL), washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (n-hexane-ethyl acetate 2:1) of the crude product gave **12** (286 mg, 39%) as a colurless oil. $[\alpha]_D$ –35.3° ($CHCl_3$). The product had the same spectral characteristics as noted above.

1-O-(2'-Hydroxy-3'-azidopropyl)-2,3:4,5-di-O-isopropylidene-β-D-fructopyranose (13)

Method (a): [15] **(*via* oxirane 12)**

Compound **12** (286 mg, 0.905 mmol) in 2-methoxyethanol / water 3:1 (20 mL) was treated with sodium azide (235 mg, 3.620 mmol, 4.0 eq) and ammonium sulfate (478 mg, 3.62 mmol, 4.0 eq) and set aside at 50°C for 12 hr. The reaction mixture was treated with water (20 mL) and ether (50 mL), and the aqueous layer extracted with ether (2x25 ml). The combined organic extracts were washed with 10% aqueous sodium chloride solution (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (n-hexane-ethyl acetate, 2:1) of the crude material gave compound **13** (289.4 mg, 88.9%) as a colourless oil. $[\alpha]_D$ –32.1° ($CHCl_3$): ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 108.95, 108.52 [*C*-$(CH_3)_2$], 102.36, 102.32 (C-2), 73.91, 73.66 (C-1, C-1'), 70.75, 70.39, 70.05, 69.47 (C-2', C-3, C-4, C-5), 60.94 (C-6), 53.02 (C-3'), 26.36, 25.66, 25.17, 23.80 (isopropylidene C) ppm. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 4.60 (dd, 1H, $J_{3,4}$ = 2.56 Hz, H-4), 4.33 (d 1H, J = 2.56 Hz, H-3), 4.23(d, 1H, $J_{5,4}$ = 8.8 Hz, H-5), 3.92 (m, 1H, H-2'), 3.88, 3.77 (dd, 1H, $J_{5,6ax}$ = 1.6 Hz, H-6ax), 3.75-3.63 (m, 4H, H-6eq, H-1, H-1'), 3.59, 3.54(dd, 1H, $J_{1',2'}$ = 7.51 Hz, H-1'), 3.57, 3.52(dd, 2H, J = 6.08 Hz, H-3'), 3.17(s, 1H, O*H*), 1.54, 1.49, 1.40, 1.34 (4s, each 3H, CMe_2) ppm.

Method (b): [10] **(*via* cyclic carbonate 11)**

Compound **4** (403 mg, 1.20 mmol) in dimethyl carbonate (15 mL) was treated with DBU (0.27 mL, 1.8 mmol, 1.5 eq) and heated at 80°C for 12 hr. Concentration of the reaction mixture *in vacuo*, followed by purification of the crude material (column chromatography, n-hexane-ethyl acetate, 1:1) gave **11** (374.3 mg, 86.6%) as a colourless oil. $[\alpha]_D$ –23.9° ($CHCl_3$): ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 154.62 (CO), 108.89, 108.72 [*C*-$(CH_3)_2$], 102.08, 102.02 (C-2), 73.26, 73.21 (C-1, C-1'), 70.86, 69.92, 69.89 (C-3, C-4, C-5), 65.97, 65.86 (C-2'), 60.07 (C-6), 61.02 (C-3'), 26.44, 25.81, 25.12, 23.89 (isopropylidene C) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 4.86-4.78 (m, 1H, H-2'), 4.60, 4.58 (dd, 1H, $J_{3,4}$ = 2.64 Hz, H-4), 4.33 (d, 1H, J = 2.7 Hz, H-3), 4.22 (d, 1H, $J_{5,4}$ = 7.9 Hz, H-5), 3.92, 3.88 (dd, 1H, $J_{5,6a}$ = 1.8 Hz, H-6a), 3.76-3.59 (m, 6H, H-6e, H-1, H-1', H-3'), 1.53, 1.46, 1.38, 1.33(4s, each 3H, CMe_2) ppm.

A stirred solution of **11** (145 mg, 0.4 mmol) in *N, N* dimethylformamide (10 mL) and water (0.4 mmol, 7.1 mL) was treated with sodium azide (104 mg, 1.6 mmol, 4 eq) at 80°C for five days. The mixture was treated with water (20 mL) and ether (50 mL). The separated organic layer was washed with 10% aqueous sodium chloride solution, dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (n-hexane-ethyl acetate, 2:1) to give the azido alcohol **13** (46.2 mg, 32%) as a colourless oil. $[\alpha]_D$ –32.3° ($CHCl_3$). The product had the same spectral characteristics as noted above.

1-O-(2'-Hydroxy-3'-aminopropyl)-2,3:4,5-di-O-isopropylidene-β-D-fructopyranose (14)

A solution of **13** (1.202 g, 3.348 mmol) in pyridine (10 mL) was treated with triphenylphosphine (1.756 g, 6.696 mmol, 2.0 eq). The reaction mixture was set aside at room

temperature until evolution of nitrogen ceased. Ammonium solution (25%, 2 mL) was added and stirring was continued for 12 hr. The mixture was concentrated *in vacuo* and column chromatography (CH_2Cl_2-MeOH, 20:1) of the residue gave **14** (856 mg, 76.8%) as a colourless oil. $[\alpha]_D$ –21.4° ($CHCl_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 108.92, 108.48 [*C*-$(CH_3)_2$], 102.46 (C-2), 73.54, 73.05 (C-1, C-1'), 70.81, 70.66, 70.54, 70.05 (C-2', C-3, C-4, C-5), 60.96 (C-6), 43.96 (C-3'), 26.44, 25.71, 25.21, 23.85 (isopropylidene C) ppm. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 4.60, 4.58 (dd, 1H, $J_{3,4}$ = 2.35 Hz, H-4), 4.34 (d 1H, J = 2.32 Hz, H-3), 4.23 (d, 1H, $J_{5,4}$ = 7.9 Hz, H-5), 3.91, 3.88 (dd, 1H, $J_{5,6ax}$ = 1.7 Hz, H-6ax), 3.80-3.56 (m, 5H, H-6eq, H-1, H-1', H-2'), 3.50, 3.47 (dd, 1H, $J_{1',2'}$ = 7.3 Hz, H-1'), 2.84, 2.80 (dd, 1H, J = 3.7 Hz, H-3'), 2.72, 2.69 (dd, 1H, J = 7.1 Hz, H-3'), 2.40 (bs, 3H, O*H*, NH_2), 1.54, 1.49, 1.40, 1.34 (4s, each 3H, CMe_2) ppm.

In another experiment compound **13** (351.2 mg, 0.978 mmol) in dry ether (10 mL) was treated with lithium aluminium hydride (130 mg, 3.42 mmol, 3.5 eq) at room temperature until analysis (TLC, n-hexane-ethyl acetate, 2:1) indicated disappearance of the starting material. The reaction was quenched by addition of ether (10 mL) and water (0.5 mL), filtered through $MgSO_4$, and concentrated *in vacuo*. Column chromatography (CH_2Cl_2 - MeOH, 20:1) of the crude product gave **14** (223.3 mg, 68.4%) as a colourless oil. $[\alpha]_D$ –21.3° ($CHCl_3$). The spectral characteristics of the product were identical to those noted above.

1-O-(2'-Hydroxy-3'-dodecanoylamidopropyl)-2,3:4,5-di-O-isopropylidene-β-D-fructopyranose (15)

A stirred, cooled (0°C) solution of **14** (601.4 mg, 1.806 mmol) in dichloromethane (10 mL) and triethylamine (0.6 mL) was treated with lauroyl chloride (0.42 mL, 1.98 mmol, 1.1 eq) for 0.5 hr. The mixture was diluted with dichloromethane (50 mL) and washed, successively with aqueous 2N hydrochloric acid (20 mL), water (20 mL) and a solution of saturated sodium hydrogen carbonate (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (n-hexane-ethyl acetate, 2:1) of the crude material gave **15** (747.4 mg, 82%) as a colourless oil. $[\alpha]_D$ –26.4° ($CHCl_3$). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 174.26, 174.04 (*C*=O), 108.87, 108.43 [*C*-$(CH_3)_2$], 102.37, 102.33 (C-2), 74.02, 73.74, 73.70, 73.28 (C-1, C-1'), 70.73, 70.64, 70.60, 70.01, 69.4 (C-2', C-3, C-4, C-5), 60.94, 60.89 (C-6), 42.39 (C-3'), 36.52,36.49 ($COCH_2$), 31.77 ($COCH_2CH_2$), 29.49-22.54 (aliphatic C and isopropylidene C), and 15.13, 13.98 (CH_3) ppm. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 6.23, 6.18 (t, 1H, J = 5.6 Hz N*H*CO), 4.60, 4.58 (dd, 1H, $J_{3,4}$ = 2.41 Hz, H-4), 4.30 (d 1H, J = 2.51 Hz, H-3), 4.23 (d, 1H, $J_{5,4}$ = 7.9 Hz, H-5), 3.91, 3.88 (dd, 1H, $J_{5,6ax}$ = 1.7 Hz, H-6ax), 3.76-3.45 (m, 5H, H-6eq, 1, H-1', H-2') 3.26 (m, 1H, H-1'), 2.84, 2.80 (dd, 1H, J = 3.7 Hz, H-3'), 2.18 (m, 2H, $COCH_2CH_2$), 1.53, 1.48, 1.41 1.40 (4s, each 3H, CMe_2), 1.28 (m, aliphatic H), 0.87 (t, 3H, CH_3) ppm.

1-O-(2'-Hydroxy-3'-tetradecanoylamidopropyl)-2,3:4,5-di-O-isopropylidene-β-D-fructo-pyranose (16)

Compound **16** (668 mg, 81%) was prepared starting from **14** (520 mg, 1.561 mmol) and tetradecanoyl chloride (424.1 mg, 1.717 mmol, 1.1 eq), using the procedure described above, to give **16**. $[\alpha]_D$ –24.9° ($CHCl_3$). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 174.29, 174.06 (*C*=O), 108.97, 108.52 [*C*-$(CH_3)_2$], 102.44, 102.39 (C-2), 74.05, 73.94, 73.63, 73.38 (C-1, C-1'), 70.78, 70.69, 70.50, 70.05, 69.42 (C-2', C-3, C-4, C-5), 60.98, 60.52 (C-6), 42.35 (C-3'), 36.65, 36.50 ($COCH_2$), 31.87 ($COCH_2CH_2$), 29.60-22.64 (aliphatic C and isopropylidene C), and, 14.08

(CH_3) ppm. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 6.22, 6.19 (t, 1H, J = 5.6 Hz N*H*CO), 4.62, 4.57 (dd, 1H, $J_{3,4}$ = 2.41 Hz, H-4), 4.31 (d 1H, J = 2.51 Hz, H-3), 4.24 (d, 1H, $J_{5,4}$ = 7.9 Hz, H-5), 3.90, 3.89 (dd, 1H, $J_{5,6ax}$ = 1.7 Hz, H-6ax), 3.76-3.44 (m, 5H, H-6eq, 1, H-1', H-2') 3.25 (m, 1H, H-1'), 2.85, 2.81 (dd, 1H, J = 3.7 Hz, H-3'), 2.19 (m, 2H, COCH_2CH$_2$), 1.52, 1.48, 1.42 1.41 (4s, each 3H, CMe_2), 1.29 (m, aliphatic H), 0.87 (t, 3H, CH_3) ppm.

1-O-(2'-Hydroxy-3'-hexadecanoylamidopropyl)-2,3:4,5-di-O-isopropylidene-β-D-fructo-pyranose (17)

Compound **17** (603 mg, 62%) was prepared starting from **14** (567 mg, 1.702 mmol) and hexadecanoyl chloride (514.8 mg, 1.872 mmol, 1.1 eq) using the same procedure as described for the synthesis of compound **15**. $[\alpha]_D$ –26.9° ($CHCl_3$). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 174.27, 174.04 (*C*=O), 108.48, 108.40 [*C*-(CH_3)$_2$], 102.41, 102.35 (C-2), 74.04, 73.85, 73.66, 73.34 (C-1, C-1'), 70.75, 70.69, 70.66, 70.05, 69.46 (C-2', C-3, C-4, C-5), 60.99, 60.46 (C-6), 42.37 (C-3'), 36.65, 36.59 (COCH_2), 31.83 (COCH$_2$CH_2), 29.60-22.61 (aliphatic C and isopropylidene C), and, 14.04 (CH_3) ppm. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 6.22, 6.18 (t, 1H, J = 5.6 Hz N*H*CO), 4.60, 4.57 (dd, 1H, $J_{3,4}$ = 2.41 Hz, H-4), 4.31 (d 1H, J = 2.51 Hz, H-3), 4.23 (d, 1H, $J_{5,4}$ = 7.9 Hz, H-5), 3.91, 3.89 (dd, 1H, $J_{5,6ax}$ = 1.7 Hz, H-6ax), 3.76-3.46 (m, 5H, H-6eq, 1, H-1', H-2') 3.24 (m, 1H, H-1'), 2.85, 2.82 (dd, 1H, J = 3.7 Hz, H-3'), 2.19 (m, 2H, COCH_2CH$_2$), 1.54, 1.47, 1.42 1.41 (4s, each 3H, CMe_2), 1.28 (m, aliphatic H), 0.87 (t, 3H, CH_3) ppm.

1-O-(2'-p-Toluenesulfonyloxy-3'-azidopropyl)-2,3:4,5-di-O-isopropylidene-β-D-fructopyranose (18)

A cooled (0°C), stirred solution of compound **13** (914 mg, 2.545 mmol) in dry pyridine (5 mL) was treated with *p*-toluenesulfonyl chloride (1.403 mg, 7.635 mmol, 3.0 eq) and set aside at room temperature for 24 hr. The reaction mixture was poured in ice water and left for 1 hr, diluted with dichloromethane (50 mL) and the separated organic layer washed successively with aqueous hydrochloric acid (2N, 20 mL), water (20 mL), saturated aqueous sodium hydrogen carbonate (20mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (n-hexane-ethyl acetate, 3:1) of the crude material gave **18** (1.1722 g, 84.2%) as a colourless oil. $[\alpha]_D$ –20.7° ($CHCl_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 129.83, 127.83 (aromatic-C), 108.90, 108.86, 108.57, 108.53 [*C*-(CH_3)$_2$], 102.14 (C-2), 73.20, 73.07 (C-1, C-1'), 70.82, 70.32, 70.00, 69.95 (C-2', C-3, C-4, C-5), 60.98 (C-6), 51.04 (C-3'), 26.44, 25.82, 25.26, 23.95 (isopropylidene C), and 21.61 (ArCH_3) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.82 (d, 2H, J = 8.31 Hz, aromatic H), 7.35(d, 2H, J = 8.19 Hz, aromatic H), 4.59-4.55 (m, 1H, H-4), 4.23 (d 1H, J = 2.66 Hz, H-3), 4.21 (m, 1H, H-5), 3.90, 3.85 (dd, 1H, $J_{5,6ax}$ = 1.7 Hz, H-6ax), 3.80-3.42 (m, 8H, H-6eq, H-1, H-1' H-3', H-2'), 2.45 (s, 3H, ArCH_3), 1.51, 1.45, 1.36, 1.34 (4s, each 3H, CMe_2) ppm.

1-O-(2',3'-Aziridinopropyl)-2,3:4,5-di-O-isopropylidene-β-D-fructopyranose (19)

A cooled (0°C), stirred solution of **18** (1.0 g, 1.949 mmol) in freshly distilled tetrahydrofuran (10 mL) was treated with lithium aluminium hydride (259.26 mg, 6.823 mmol, 3.5 eq) and then kept at room temperature for 20-30 mins. The reaction mixture was quenched by addition of ether (20 mL) and water (0.5mL), filtered through $MgSO_4$, and concentrated *in vacuo*. Column chromatography (methanol-dichloromethane, 1:9) of the crude product gave **19** (378.3 mg, 61.5%) as a colourless oil. $[\alpha]_D$ –28.8° ($CHCl_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz)

δ 108.82, 108.44 [*C*-$(CH_3)_2$], 102.49 (C-2), 72.59, 72.54, 72.49 (C-1, C-1'), 70.90, 70.08, 69.97, 69.94 (C-3, C-4, C-5), 60.92 (C-6), 28.98 (C-2'), 22.67, 22.43 (C-3'), 26.46, 25.78, 25.22, 23.93 (isopropylidene C) ppm. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 4.60 (dd, 1H, $J_{3,4}$ = 2.56 Hz, H-4), 4.38 (d 1H, J = 2.57 Hz, H-3), 4.20 (d, 1H, $J_{5,4}$ = 8.8 Hz, H-5), 3.92, 3.88 (dd, 1H, $J_{5,6ax}$ = 1.8 Hz, H-6ax), 3.72-3.62 (m, 4H, H-6eq, H-1, H-1'), 3.43-3.40 (dd, 1H, H-1'), 2.20 (m, 1H, H-2'), 1.77 (d, 2H, H-3'), 1.53, 1.48, 1.43, 1.34 (4s, each 3H, CMe_2) ppm.

1-O-*(2',3'*-N-*dodecanoylaziridinopropyl)-2,3:4,5-di*-O-*isopropylidene*-β-**D**-*fructopyranose (20)*

A stirred, cooled (–18°C) solution of **19** (378.3 mg, 1.2 mmol) in dichloromethane (5 mL) containing triethyamine (0.26 mL, 2.5 eq) was treated with lauroyl chloride (0.30 mL, 1.32 mmol, 1.1 eq) and set aside for 2 hr. The reaction mixture was diluted with dichloromethane (10 mL) and washed with 10% (w / w) citric acid (10 mL). The organic extract was dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (n-hexane-ethyl acetate, 2:1) of the crude material gave **20** (508 mg, 85%) as a colourless oil. $[\alpha]_D$ –29.4° ($CHCl_3$). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 185.81 (*C*=O), 108.89, 108.55 [*C*-$(CH_3)_2$], 102.46 (C-2), 72.64, 72.61, 72.54, 72.13 (C-1, C-1'), 70.94, 70.12, 70.00, 69.97 (C-2', C-3, C-4, C-5), 61.02 (C-6), 36.63 (C-3'), 35.41 (C-2'), 31.86 ($COCH_2$), 29.56-22.64 (aliphatic C and isopropylidene C), and 14.07 (CH_3) ppm. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 4.61 (dd, 1H, $J_{3,4}$ = 2.6 Hz, H-4), 4.39 (d 1H, J = 2.65 Hz, H-3), 4.24 (d, 1H, $J_{5,4}$ = 7.9 Hz, H-5), 3.93, 3.89 (dd, 1H, $J_{5,6ax}$ = 1.7 Hz, H-6ax), 3.75-3.62 (m, 4H, H-6eq, H-1, H-1'), 3.57 (dd, 1H, J = 6.11 Hz, H-1'), 2.68-2.66 (m, 1H, H-2'), 2.43-2.34 (m, 2H, $COCH_2$), 2.13 (dd, 1H, J = 3.32 Hz, H-3'), 1.55, 1.46, 1.44, 1.35 (4s, each 3H, CMe_2), 1.29 (m, aliphatic H), 0.88 (t, 3H, CH_3) ppm.

1-O-*(2',3'*-N-*tetradecanoylaziridinopropyl)-2,3:4,5-di*-O-*isopropylidene*-β-**D**-*fructopyranose (21)*

Compound **21** was prepared starting from **19** (382 mg, 1.212 mmol) and myristic chloride (0.4 mL, 1.33 mmol, 1.1 eq) using the same procedure as described for the synthesis of compound **20**. Column chromatography (n-hexane-ethyl acetate, 2:1) of the crude material gave **21** (470 mg, 74%) as a colourless oil. $[\alpha]_D$ –28.8° ($CHCl_3$) ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 185.75 (*C*=O), 108.86, 108.84, 108.51 [*C*-$(CH_3)_2$], 102.43 (C-2), 72.61, 72.56, 72.50, 72.08 (C-1, C-1'), 70.90, 70.09, 69.97, 69.93 (C-2', C-3, C-4, C-5), 60.98 (C-6), 36.59 (C-3'), 35.37 (C-2'), 31.83 ($COCH_2$), 29.60-22.64 (aliphatic C and isopropylidene C), and 14.04 (CH_3) ppm. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 4.60 (dd, 1H, $J_{3,4}$ = 2.6 Hz, H-4), 4.38 (d 1H, J = 2.65 Hz, H-3), 4.23 (d, 1H, $J_{5,4}$ = 7.9 Hz, H-5), 3.92, 3.89 (dd, 1H, $J_{5,6ax}$ = 1.7 Hz, H-6ax), 3.74-3.62 (m, 4H, H-6eq, H-1, H-1'), 3.56 (dd, 1H, J = 6.11 Hz, H-1'), 2.67-2.66 (m, 1H, H-2'), 2.42-2.34 (m, 2H, $COCH_2$), 2.12 (dd, 1H, J = 3.32 Hz, H-3'), 1.54, 1.46, 1.44, 1.35 (4s, each 3H, CMe_2), 1.28 (m, aliphatic H), 0.88 (t, 3H, CH_3) ppm.

1-O-*(2',3'*-N-*hexadecanoylaziridinopropyl)-2,3:4,5-di*-O-*isopropylidene*-β-**D**-*fructopyranose (22)*

Compound **22** was obtained from **19** (280 mg, 0.88 mmol) and palmitoyl chloride (0.29 mL, 0.977 mmol, 1.1 eq), using the procedure described above. Column chromatography (n-hexane-ethyl acetate, 2:1) of the crude material gave **22** (427 mg, 88%) as a colourless oil. $[\alpha]_D$ –26.8° ($CHCl_3$). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 185.80 (*C*=O), 108.90, 108.55 [*C*-$(CH_3)_2$], 102.46 (C-2), 72.65, 72.61, 72.54, 72.13 (C-1, C-1'), 70.94, 70.12, 70.01, 69.97 (C-2', C-3, C-4, C-5), 61.02 (C-6), 36.63 (C-3'), 35.40 (C-2'), 31.88 ($COCH_2$), 29.58-22.64 (aliphatic C and isopropylidene C), and 14.08 (CH_3) ppm. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 4.59 (dd, 1H, $J_{3,4}$ = 2.6

Hz, H-4), 4.37 (d 1H, J = 2.65 Hz, H-3), 4.22 (d, 1H, $J_{5,4}$ = 7.9 Hz, H-5), 3.92, 3.89 (dd, 1H, $J_{5,6ax}$ = 1.7 Hz, H-6ax), 3.73-3.62 (m, 4H, H-6eq, H-1, H-1'), 3.55 (dd, 1H, J = 6.11 Hz, H-1'), 2.66-2.66 (m, 1H, H-2'), 2.43-2.34 (m, 2H, $COCH_2$), 2.11 (dd, 1H, J = 3.32 Hz, H-3'), 1.53, 1.46, 1.44, 1.35 (4s, each 3H, CMe_2), 1.27 (m, aliphatic H), 0.88 (t, 3H, CH_3) ppm.

9.5 References

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SUMMARY

This thesis describes the synthesis of some glyceryl derivatives of **D**-fructose. Glyceroglycolipids are found in plants, animal tissues, and in many kind of bacteria. They have various functions including mediation of the cell surface recognition, synthesis of fatty acids, electron transport, as carbohydrate reservoirs, and energy storage etc. These also exhibit several interesting biological activities including *in vitro* and *in vivo* tumour inhibitory activity. The nature of the carbohydrate moiety of glycosylglycerols was found to have an influence on cancer chemoprevention activity. Apart from the above mentioned functions and biological properties, these compounds have other properties. e.g amphiphilic activity.

Glyceroglycolipids, and other related compounds, are often obtained from natural sources but in very small quantities. Chemical synthesis is an altenative method which could supply larger amount of these compounds for biological studies, and other applications.

D-Fructose is one of the most naturally abundant carbohydrates but unlike the aldoses and other ketohexoses, it exhibits complex mutarotational behaviour in many of the solvents commonly used in reactions. As a result, glycosidation of **D**-fructose under Fischer-type conditions usually affords mixtures of the four fructosides. Separation of these mixtures by chromatography is cumbersome and in most cases gives poor yields. The use of Koenigs-Knorr conditions is fraught with difficulties and does notprovide alternative reaction posibilities.

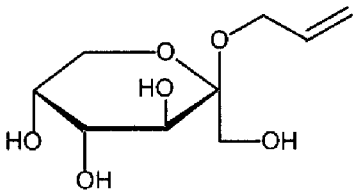
It is surprising that there are not more natural products containing **D**-fructose linked glycosidically to a variety of alternative aglycons in view of its natural abundance. Few examples of **D**-fructose occuring naturally in the pyranose form have been described, despite it being that of the pure crystalline form. So far, lipid structures containing a **D**-fructose unit have not been reported. The fructosyl glycolipid derivatives described here could have interesting biological and amphiphilic properties.

Chapter 1 gives a general introduction to carbohydrates, glycosidic glycerols and other related compounds.

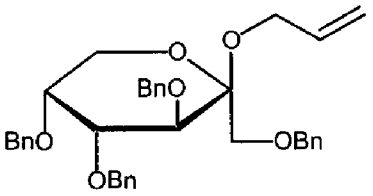
In **chapter 2** a literature review of simple glycolipids (glycosyl glycerols) and related compounds, with special reference to the various synthetic approaches that have been used to synthesize these compounds, is presented.

Chapter 3 describes the synthesis of some dihydroxypropyl β-**D**-fructopyranoside derivatives starting from allyl β-**D**-fructopyranoside (**1**). During the synthesis of these compounds, the hydroxyl groups of the fructosyl moiety were suitably protected as *O*-benzyl ether functions which were removed in the later stages by catalytic hydrogenolysis. Investigations on chiral catalyzed asymmetric dihydroxylation reactions (Sharpless type) of **2** to

give **3** were carried out using chiral ligands based on phthalazine (PHAL), pyrimidine (PYR), and anthraquinone (AQN). The dihydroquinine based pyrimidine ligand $(DHQ)_2PYR$ gave products with higher diastereomeric selectivity. Compound **3** was obtained in its pure form by selective crystallization, and was employed in many subsequent transformations. The stereochemistry of the generated glycerol moiety in compound **3** was established by formation of the known dibenzyl glycerol derivative **4** formed from **3** by a benzylation / hydrolysis sequence. Comparison of the ^{1}H-NMR and ^{13}C-NMR spectra and optical rotation values of **4** with the values reported earlier for the pure derivative permitted assignment of the *R* configuration at C-2 of the aglycon on **3**. Synthesis of di-*O*-acyl ester derivatives were carried out using fatty acid chlorides (lauroyl, myristoyl, and palmitoyl). The yields of the obtained products were satisfactory. The debenzylated derivatives **5-7** were obtained by catalytic hydrogenolysis (H_2, Pd/C) of the resultant products.



1



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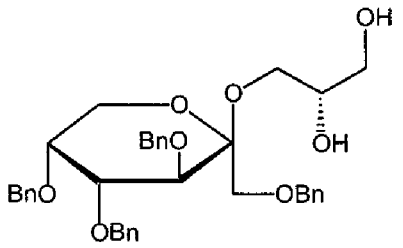

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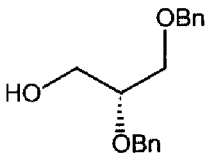

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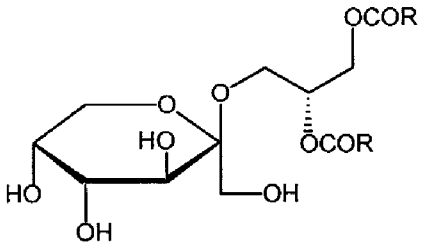
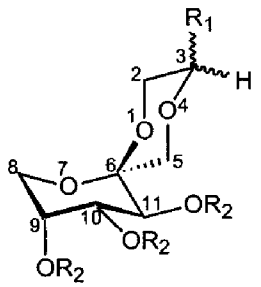


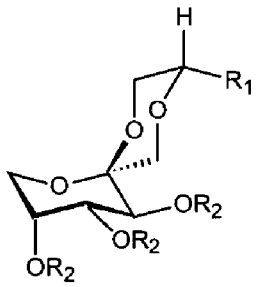
5-7

R = C_{11}, C_{13}, C_{15}

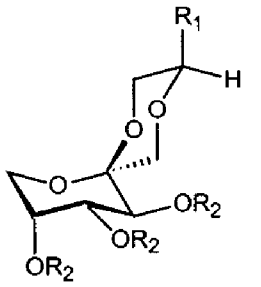
Chapter 4 describes the synthesis of some bicyclic derivatives obtained by reductive ozonolysis of allyl β-fructopyranoside (**1**) to yield **8**. Compound **8** was a mixture of two isomers. The spiro-fructosides **9** and **10** were obtained as a mixture (1:2) when compound **8** was acetylated (acetic anhydride-pyridine) in the usual manner. Acetylation of **8** using acetic anhydride - sodium acetate gave a mixture of **9** and **10** in a 1:3 ratio. Compounds **9** and **10** were separated by column chromatography. Based on X-ray diffraction studies, compound **9** was the α isomer and the C-3 acetoxy group was assigned the *R*-configuration. Compound **10**, likewise, was the β derivative and the C-3 acetoxy group the *S*-configuration. All other subsequent conversions to obtain quasi di-and trisaccharide analogues were performed using compounds **8**, **9** and **10**.



8 R_1 = OH, R_2 = H

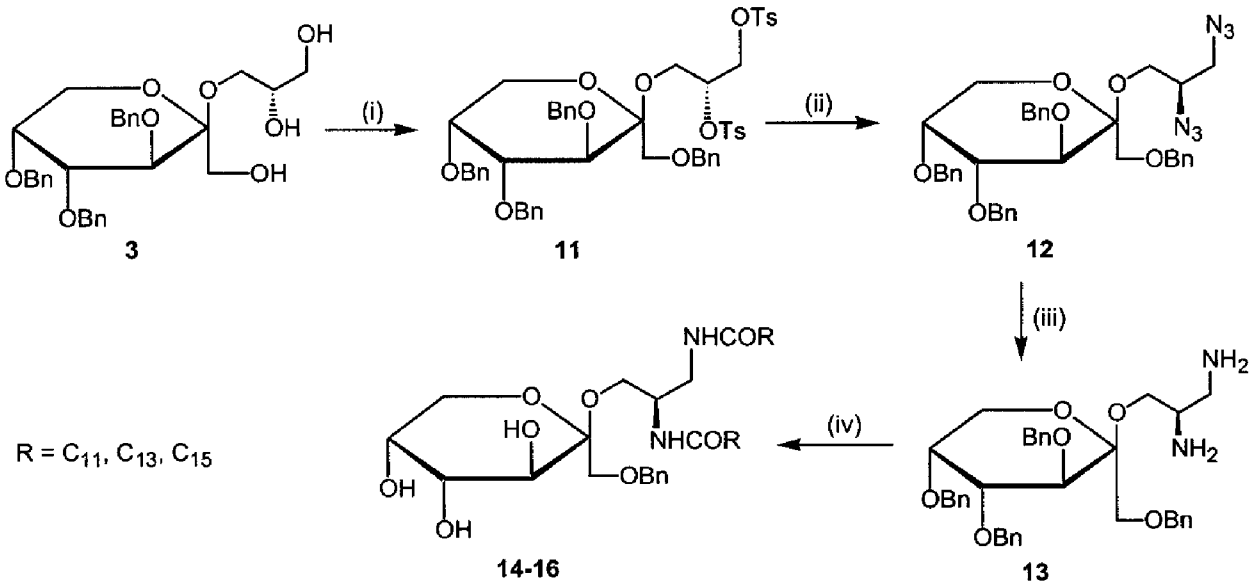


9 R_1 = OAc, R_2 = Ac



10 R_1 = OAc, R_2 = Ac

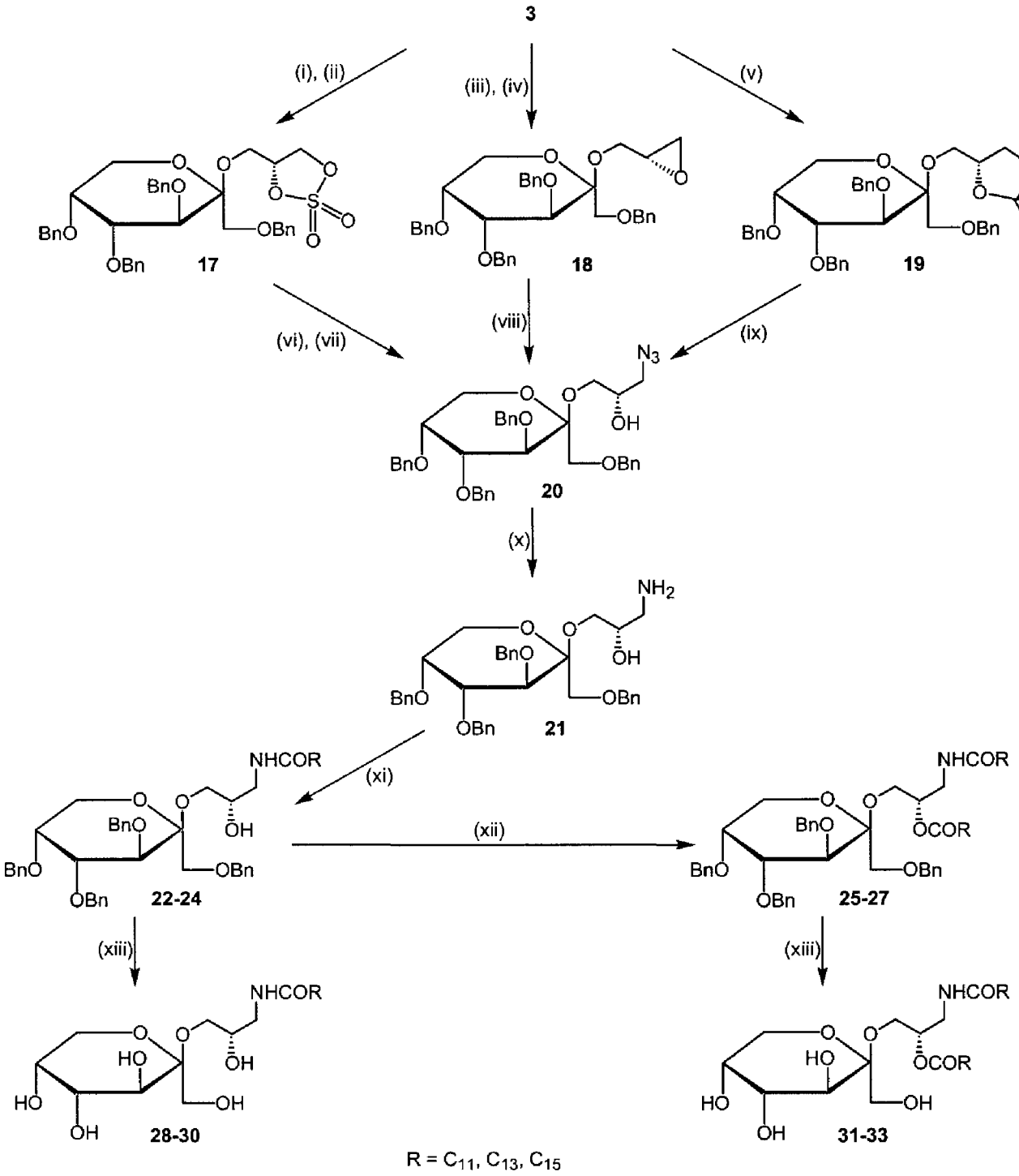
Chapter 5 describes the synthesis of some long-chain mono acylamino derivatives and bis-acylamino compounds from the diol **3**. The synthesis of the bis-amide derivatives **14-16** is depicted in Scheme 1.



Scheme 1

Compound **20** was the important intermediate for the synthesis of mono acylamino derivatives and was obtained using three synthetic routes based on a cyclic sulfate **17**, an oxirane **18** or cyclic carbonate **19** as intermediates (Scheme 2).

Reduction of **20** gave amino alcohol **21**. Controlled acylation of **21** with long-chain aliphatic acid chlorides (lauroyl, myristoyl, or palmitoyl) yielded the corresponding amides **22-24** (64-72%). Catalytic hydrogenolysis (H_2, Pd/C) of compounds **22-24** gave the fully deprotected mono amides **28-30**. Acylation of the protected amides **22-24** using the same acid chlorides at room temperature (25°C) gave the corresponding *O*-acyl derivatives **25-27**. Catalytic hydro-genolysis (H_2, Pd/C) in the same manner gave the debenzylated compounds **31-33** (Scheme 2).



(i) pTsCl / pyridine
(ii) NaN_3 / DMF / 80 °C / 12 hr
(iii) $EtC(OEt)_3$ / Me_3SiCl / CH_2Cl_2 / 0 °C
(iv) K_2CO_3 / MeOH / rt or MeONa / CH_2Cl_2 / rt
(v) $(CH_3O)_2CO$ / DBU, 80 °C / 1 hr
(vi) LiN_3 / DMF / 80 °C / 1 hr
(vii) THF / conc. H_2SO_4
(viii) NaN_3 / $(NH_4)_2SO_4$ / $CH_3OCH_2CH_2OH$ / H_2O / rt
(ix) NaN_3 / H_2O / DMF / 80-95 °C
(x) PPh_3 / pyridine / NH_3 soln.
(xi) RCOCl / CH_2Cl_2 / Et_3N / 0 °C / 1 hr
(xii) RCOCl / pyridine / DMAP / rt / 1 hr
(xii) H_2 -Pd(C) / MeOH / 2 hr

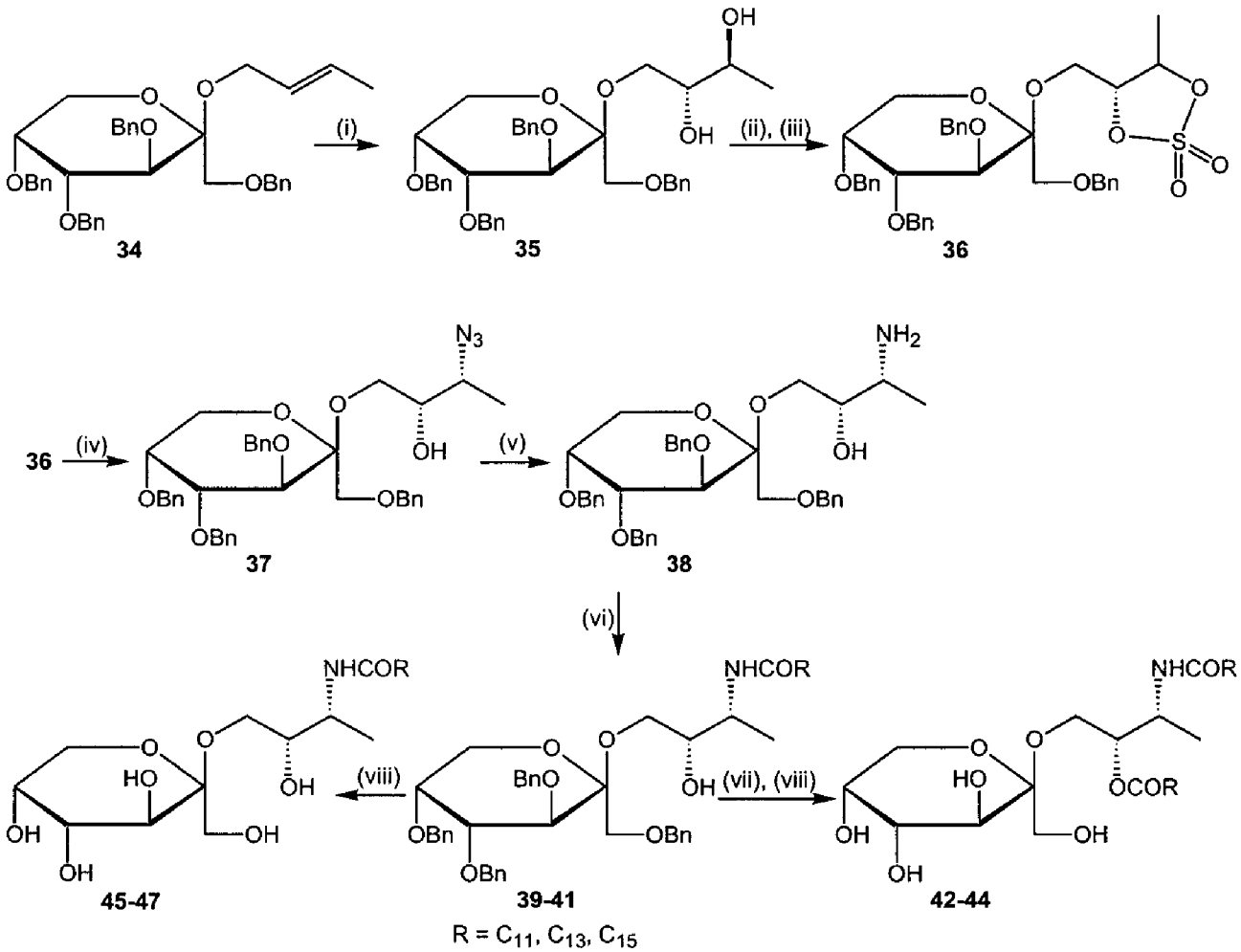
Scheme 2

In **chapter 6** the synthesis and reactions of but-2-enyl β-**D**-fructopyranoside are described. Stereoselective asymmetric dihydroxylation (Sharpless type) of benzylated but-2-enyl β-**D**-fructo-pyranoside **34** afforded crystalline **35**. The absolute configurations of the chiral

centres in the aglycon moiety of compound **35** were shown to be 2(*R*),3(*R*). Transformation of **35** into the azido alcohol **37** was achieved by ring opening of the cyclic sulfate derivative **36**.

Compound **37** was subsequently converted into the amino alcohol **38** by reduction with triphenylphosphine.

Synthesis of acylamino derivatives **39-41** from of the amino alcohol **38** was accomplished using fatty acid chlorides (lauroyl, myristoyl or palmitoyl) as the acylating agents. Reaction of **39-41** with excess of fatty acid chloride (lauroyl, myristoyl or palmitoyl) in the presence of catalytic amounts of 4-(*N,N*-dimethylamino)pyridine at room temperature (25°C), followed by catalytic hydrogenolysis (H_2, Pd/C) gave compounds **42-44**. The unprotected amide derivatives **45-47** were obtained by catalytic hydrogenolysis of compounds **39-41** in the same manner (Scheme 3).

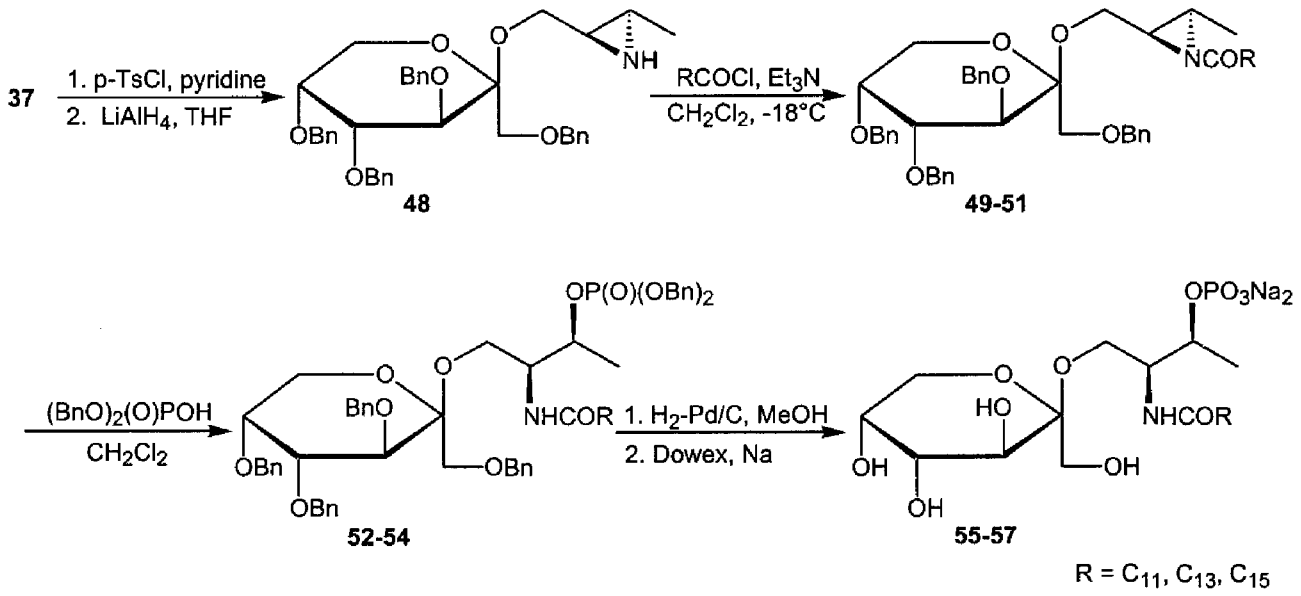


(i) $PhCH_2Cl$/DMSO/KOH
(ii) $SOCl_2/Et_3N/CH_2Cl_2$ 0°C
(iii) $CCl_4/CH_3CN/H_2O/NaIO_4/RuCl_3xH_2O$
(iv) LiN_3/DMF/80°C/1hr
(v) PPh_3/Pyridine/NH_3 soln
(vi) RCOCl/ CH_2Cl_2/Et_3N, 0°C 1hr
(vii) RCOCl/ pyridine/DMAP, RT, 1hr
(viii) H_2/Pd(C)/MeOH, 2hr

Scheme 3

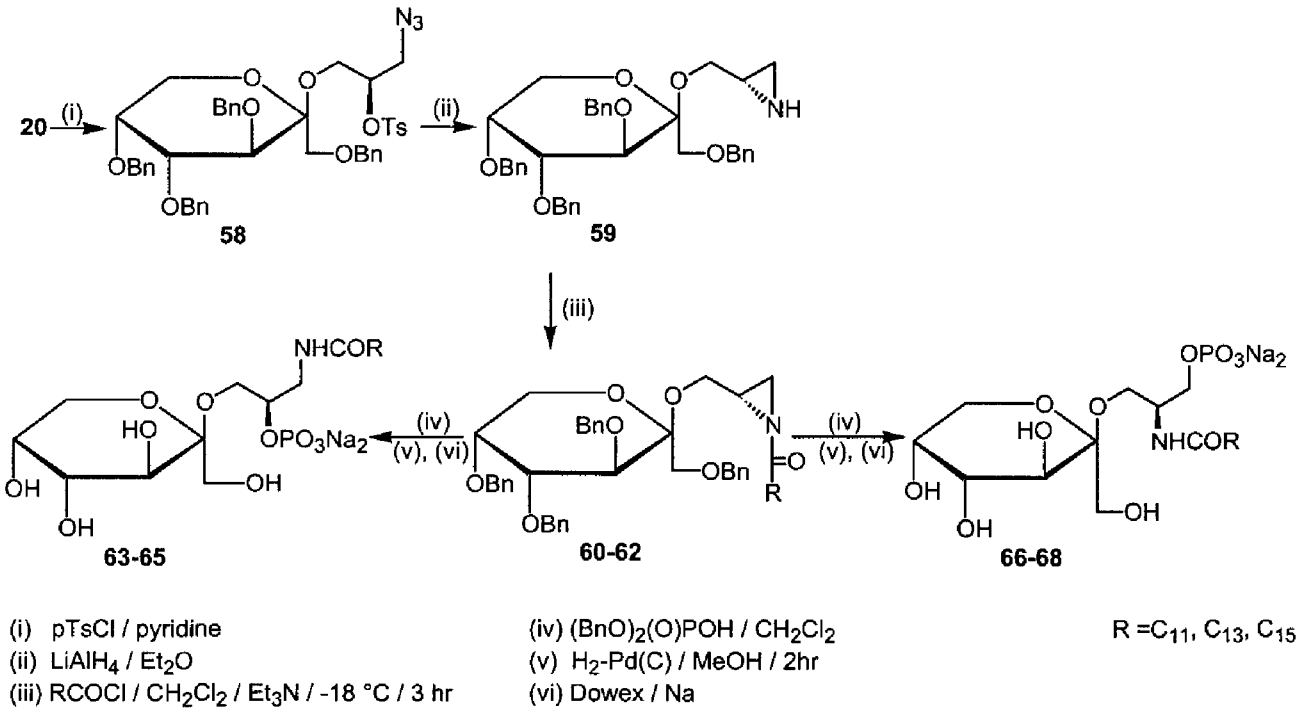
Conversion of **37** into the corresponding aziridine derivative **48** (69%) was accomplished in the usual manner. *N*-acyl aziridine derivatives **49-51** were obtained by reaction of compound **48** with the same fatty acid chlorides. Nucleophilic ring-opening of these activated derivatives

using dibenzyl hydrogen phosphate at room temperature (25°C) led to the preponderant formation of only one regio-isomer in each case. The products obtained, **52-54**, were subjected to catalytic hydrogenolysis, and were subsequently converted into the corresponding disodium salts **55-57** using ion exchange resin (Dowex-50Wx2, sodium form) (Scheme 4).



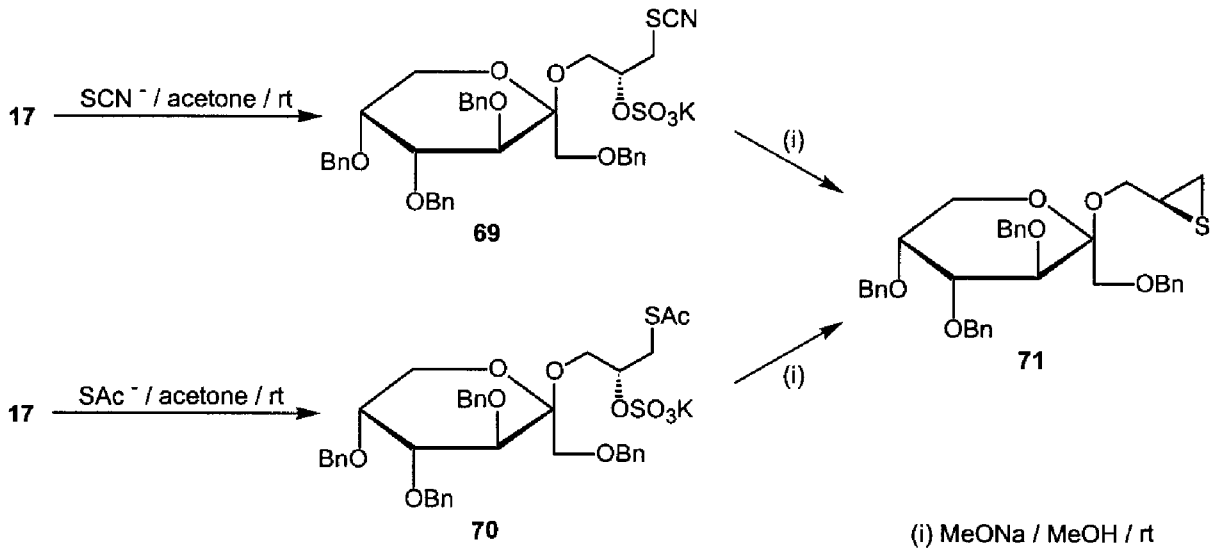
Scheme 4

In **chapter 7** investigations into the synthesis of some acylamino phosphates from 2,3-dihydroxyalkyl β-D-fructopyranoside derivatives are described. An important intermediate for the syntheses of these derivatives was compound **59** obtained from the azido alcohol **20** by sequential treatment with *p*-toluenesulfonyl chloride-pyridine and lithium aluminium hydride. Attempts to obtain compound **59** *via* a Staudinger-type reduction of the azido alcohol **20** were unsuccessful. Acylation of **59** using various fatty acid chlorides furnished the corresponding *N*-acylated aziridines **60-62** in reasonable yields. The preparation of some acylamino phosphates by ring-opening of the activated *N*-acyl aziridines **60-62** with dibenzyl hydrogen phosphate was investigated. A mixture of two compounds was obtained in each case. These were separated by column chromatography to give pure regio isomers. Conducting these reactions at -18°C for *ca* 3 hr changed the product ratio from 1:1 (at 25°C) to 4:1, 5:1, and 7:1, respectively. Catalytic hydrogenolysis (H_2, Pd/C) removed the benzyl groups and the products were converted into pure di-sodium salts by treatment with ion-exchange resin (Dowex-50Wx2, sodium form) to give the pure di-sodium salts **63-68** (Scheme 5).



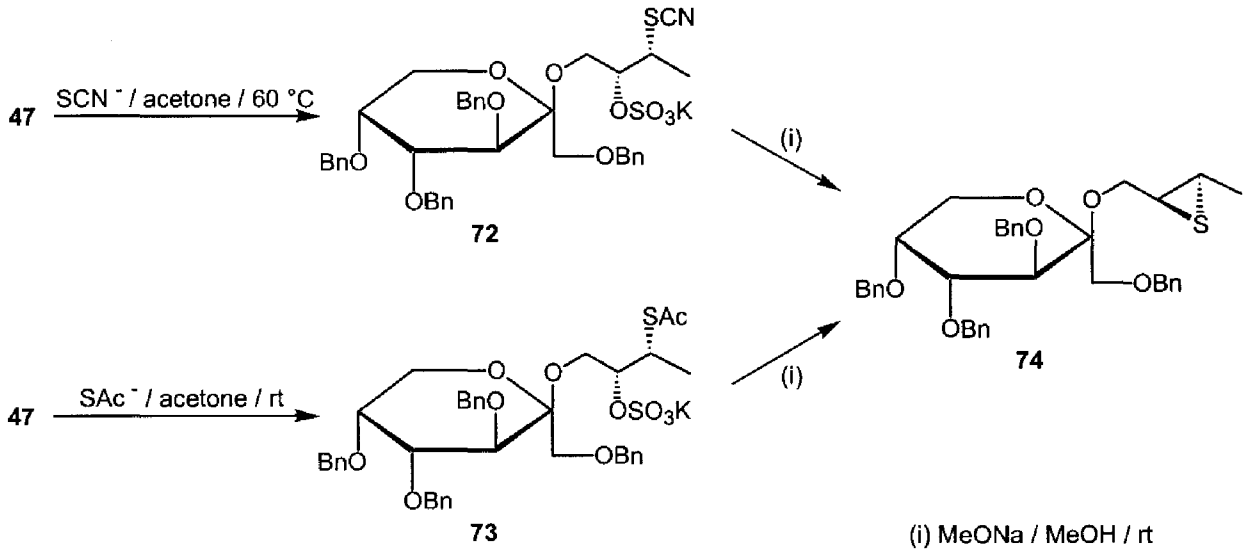
Scheme 5

Chapter 8 describes the synthesis of some epithioalkyl glycosides of D-fructose using two conventional routes. These involved reaction of compound **18** (see chapter 5) with potassium thiocyanate in aqueous ethanol or 1,4-dioxane to give the episulfide **71** (52-58%), or with thiourea in methanol to furnish **71** (90%). An alternative approach involved the use of cyclic sulfate **17** (see chapter 5) which, with potassium thiocyanate, gave the intermediate **69** (89%). The episulfide **71** (51%) was obtained when **69** was treated with a solution of sodium methoxide. Reaction of compound **17** with potassium thioacetate afforded the S-acetyl derivative **70**, which gave **71** on treatment with methanolic sodium methoxide (Scheme 6).



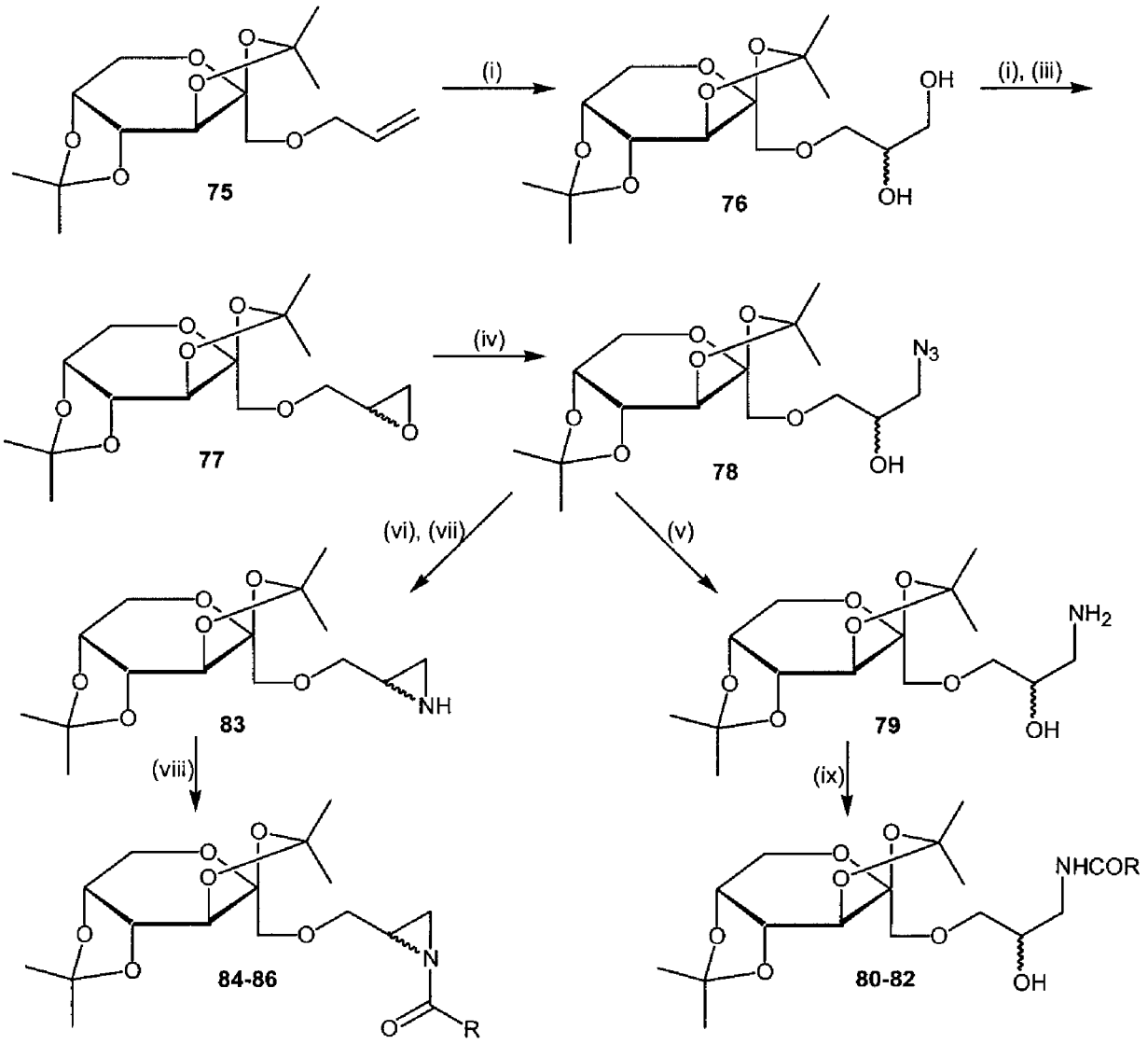
Scheme 6

Compound **74** was obtained from the cyclic sulfate **47** (see chapter 6) in a similar manner. The thiirane **74** was obtained in better yield (81%) when the cyclic sulfate **47** was treated with potassium thioacetate in acetone followed by reaction of the resultant salt **73** with sodium methoxide in methanol (scheme 7). Attempts to remove the benzyl ether protecting groups from the episulfides **71** and **74** were not successful, only partial debenzylation was observed, probably due to poisoning of the catalyst. Debenzylation using sodium metal dissolved in liquid ammonia also led to unsatisfactory results. Complex mixtures of products were formed which could not be separated.



Scheme 7

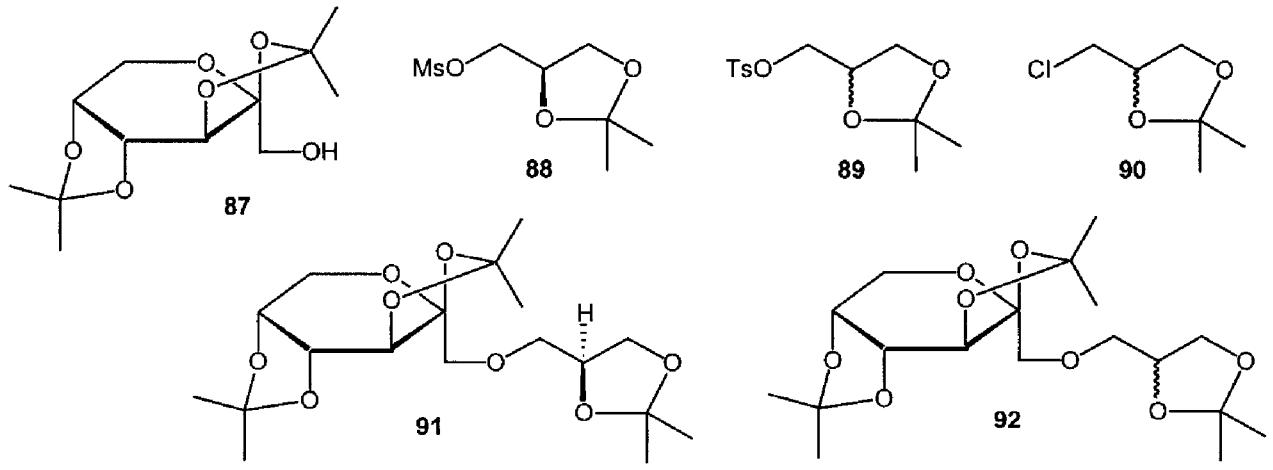
Chapter 9 describes some preliminary results on the synthesis of a 1-*O*-glyceryl ether and some related compounds from 1-O-allyl-2,3:4,5-di-*O*-isopropylidene-β-**D**-fructopyranose (**75**). The key product **76** in this sequence was obtained by simple dihydroxylation reactions of **75** using potassium permanganate or potassium (VI) osmate as oxidizing agents. Compound **76** was converted into the oxirane **77** using standard procedures. Nucleophilic ring-opening of the oxirane **77** with sodium azide gave azido alcohols **78** as a diastereomeric mixture which was converted into the amino alcohols **79** and aziridine derivatives **83**. Compounds **79** were obtained when **78** were reduced with triphenylphosphine or lithium aluminium hydride. Transformation of **78** to aziridine derivatives **83** was carried out *via* monosulfonate derivatives. Treatment of the amino alcohols **79** and the aziridine derivatives **83** with fatty acid chlorides (lauroyl, myristoyl or palmitoyl) furnished the corresponding mono-amide derivatives **80-82** and *N*-acyl aziridines **84-86** in reasonable yields. Attempts were made to obtain stereo-defined derivatives by treatment of compound **87** with the 4(*R*)-methanesulfonate derivative **88** to give compound **91**. Reaction of **87** with the racemic monotosylate **89** in the same manner gave an inseparable mixture of unreacted **89** and compound **92**. Attempts to obtain compound **92** by treatment of **87** with compound **90** were also not successful. Selective removal of the exocyclic isopropylidene groups from compounds **91** and **92** was not successful.



R = C_{11}, C_{13}, C_{15}

(i) AD-mix αor $KMnO_4$ / H_2O / acetone
(ii) $EtC(OEt)_3$ / Me_3SiCl / CH_2Cl_2 / 0 °C
(iii) K_2CO_3 / MeOH / rt or MeONa / CH_2Cl_2 / rt
(iv) NaN_3 / $(NH_4)_2SO_4$ / $CH_3OCH_2CH_2OH$ / H_2O / rt
(v) PPh_3 / pyridine / NH_3 soln. or $LiAlH_4$ / Et_2O
(vi) pTsCl / pyridine
(vii) $LiAlH_4$ / THF
(viii) RCOCl / CH_2Cl_2 / Et_3N / -18 °C / 1 hr
(ix) RCOCl / CH_2Cl_2 / Et_3N / 0 °C / 1 hr

Scheme 8



SAMENVATTING

In dit proefschrift wordt de synthese beschreven van enkele glycerylderivaten van **D**-Fructose. Glyceroglycolipiden zijn aanwezig in planten, dierlijk weefsel en in vele soorten bacteriën. Ze vervullen ondermeer een rol bij het herkennen van celoppervlakken, de synthese van vetzuren, bij elektronentransport, als koolhydraatreserves en energieopslag, etc. Glycero-glycolipiden bezitten een aantal interessante biologische activiteiten waaronder *in vitro* en *in vivo* antitumor activiteit. De aard van de koolhydraat in de glycosylglycerols blijkt van invloed te zijn op de kankerpreventie-activiteit. Naast de bovengenoemde functies en biologische eigenschappen bezitten deze verbindingen nog amfifiele eigenschappen.

Glyceroglycolipiden en hieraan gerelateerde verbindingen worden veelal in slechts kleine hoeveelheden verkregen uit natuurlijke bronnen. Chemische synthese is een alternatieve methode om grotere hoeveelheden van deze verbindingen te kunnen verkrijgen voor biologische studies en andere toepassingen. In dit proefschrift worden een aantal van zulke syntheses beschreven.

D-Fructose is één van de meest voorkomende natuurlijke koolhydraten. In tegenstelling tot aldosen en andere hexosen vertoont het echter een complex mutarotatie gedrag in de meeste van de gebruikelijke oplosmiddelen. Dit leidt ertoe dat glycosidering van **D**-fructose onder Fischer condities gewoonlijk mengsels oplevert van vier fructosiden. Scheiding van deze mengsels met behulp van chromatografie is omslachtig en geeft in de meeste gevallen slechte opbrengsten. Het gebruik van Koenigs-Knorr condities geeft vele problemen en levert geen mogelijkheden voor alternatieve reacties.

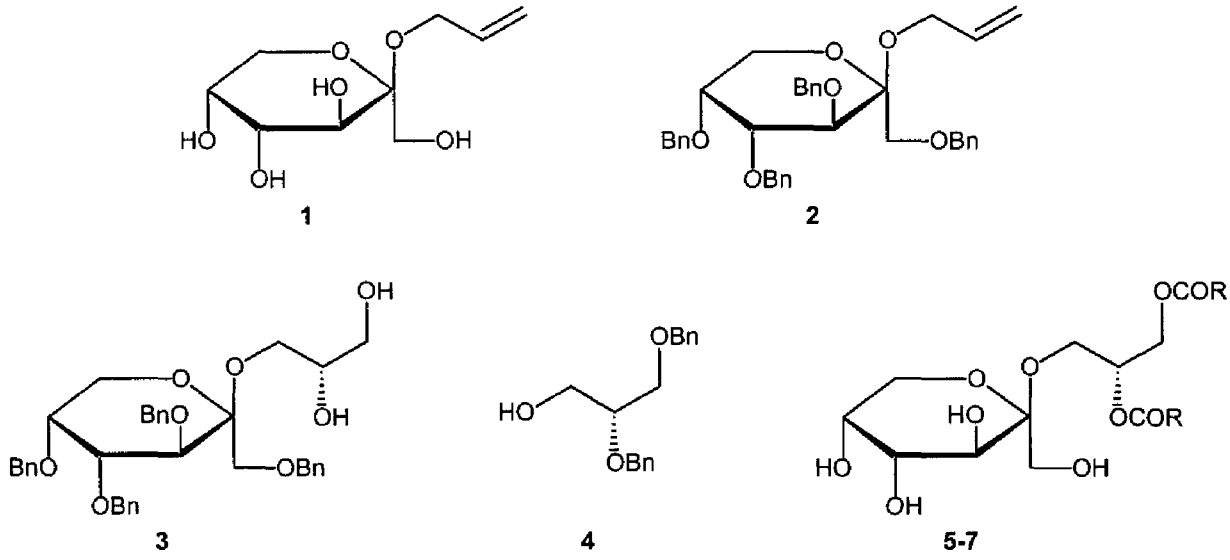
Gelet op het algemene voorkomen van **D**-fructose is het verbazingwekkend dat er niet meer natuurlijke producten bestaan waarin **D**-fructose glycosidisch is gebonden aan een verscheidenheid aan aglycons. Er zijn slechts weinig voorbeelden beschreven, waarin **D**-fructose in natuurlijke vorm voorkomt in de pyranose vorm, ondanks dat dit de vorm is waarin **D**-fructose aanwezig is in het pure kristal. Tot op heden zijn er geen **D**-fructose bevattende lipiden beschreven. De fructosylglycolipidederivaten beschreven in dit proefschrift vertonen mogelijk interessante biologische en amfifiele eigenschappen.

Hoofdstuk 1 geeft een algemene introductie over koolhydraten, glycosidische glycerolen en hieraan gerelateerde verbindingen.

Hoofdstuk 2 geeft een literatuuroverzicht van eenvoudige glycolipiden (glycosyl glycerolen) en hieraan gerelateerde verbindingen met speciale aandacht voor de verschillende synthetische benaderingen die zijn gevolgd voor de synthese van deze verbindingen.

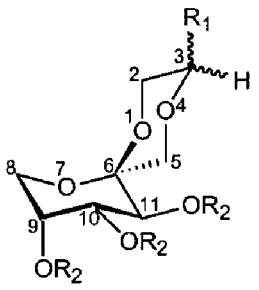
In **Hoofdstuk 3** wordt de synthese beschreven van enkele dihydroxypropyl β-**D**-fructo-pyranoside-derivaten uitgaande van allyl β-**D**-fructopyranoside (**1**). De hydroxylgroepen van de

fructose-eenheid werd tijdens de synthese van deze verbindingen beschermd als *O*-benzylethers en vervolgens in een latere fase van de synthese weer verwijderd met behulp van katalytische hydrogenering. Verder worden in dit hoofdstuk de chirale gekatalyseerde asymmetrische dihydroxyleringsreacties (Sharpless methode) van verbindingen **2** en **3** beschreven, waarbij gebruik werd gemaakt van chirale liganden gebaseerd op ftalazine (PHAL), pyrimidine (PYR) en anthrachinon (AQN). Het op pyrimidine gebaseerde dihydrokinine ligand $(DHQ)_2PYR$ leverde producten op met een hogere diastereomere selectiviteit. Verbinding **3** werd in zuivere vorm verkregen met behulp van selectieve kristallisatie en werd gebruikt in een diversiteit aan omzettingen. De stereochemie van de gevormde glyceroleenheid in verbinding **3** werd bepaald door bereiding van het bekende dibenzylglycerolderivaat **4** met behulp van een benzylering-hydrolyse procedure. Na vergelijking van de ^1H- en ^{13}C-NMR spectra en de optische rotatie van **4** met de reeds bekende waarden voor de eerder in de literatuur gerapporteerde zuivere derivaat kon de *R*-configuratie worden toegekend aan C-2 van de aglyconeenheid in **3**. Syntheses van di-*O*-acylesterderivaten werden uitgevoerd met behulp van verschillende vetzuurchlorides (lauroyl, myristoyl en palmitoyl). De opbrengsten van de verkregen producten waren redelijk. De ontschermde derivaten **5-7** werden verkregen door katalytische hydrogenering (H_2, Pd/C) van de resulterende producten.

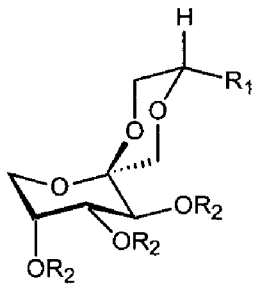


Hoofdstuk 4 is gewijd aan de synthese van enkele bicyclische verbindingen door middel van reductieve ozonolyse van allyl β-**D**-fructopyranoside (**1**). Verbinding **8** werd verkregen als een mengsel van twee isomeren. Wanneer verbinding **8** werd geacetyleerd met behulp van azijnzuuranhydride in pyridine, werden de spirofructosiden **9** en **10** verkregen als een mengsel in de verhouding 1:2. Acetylering van **8** met behulp van azijnzuuranhydride en natriumacetaat leverde een mengsel van **9** en **10** in een verhouding 1:3. Verbindingen **9** en **10** werden gescheiden met behulp van kolomchromatografie. Met behulp van Röntgen-diffractie analyse kon worden aangetoond, dat verbinding **9** de α-isomeer was en dat aan de C-3 acetoxygroep de

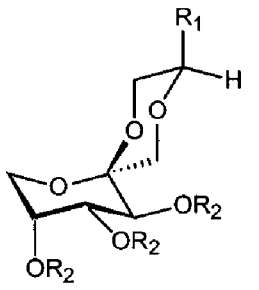
R-configuratie kon worden toegekend. In overeenstemming hiermee bleek verbinding **10** het β-derivaat te zijn, de C-3 acetoxygroep bleek de *S*-configuratie te bezitten. Alle navolgende omzettingen voor de bereiding van quasi di- en trisaccharideanaloga werden uitgevoerd met verbindingen **8**, **9** en **10**.



8 R_1 = OH, R_2 = H

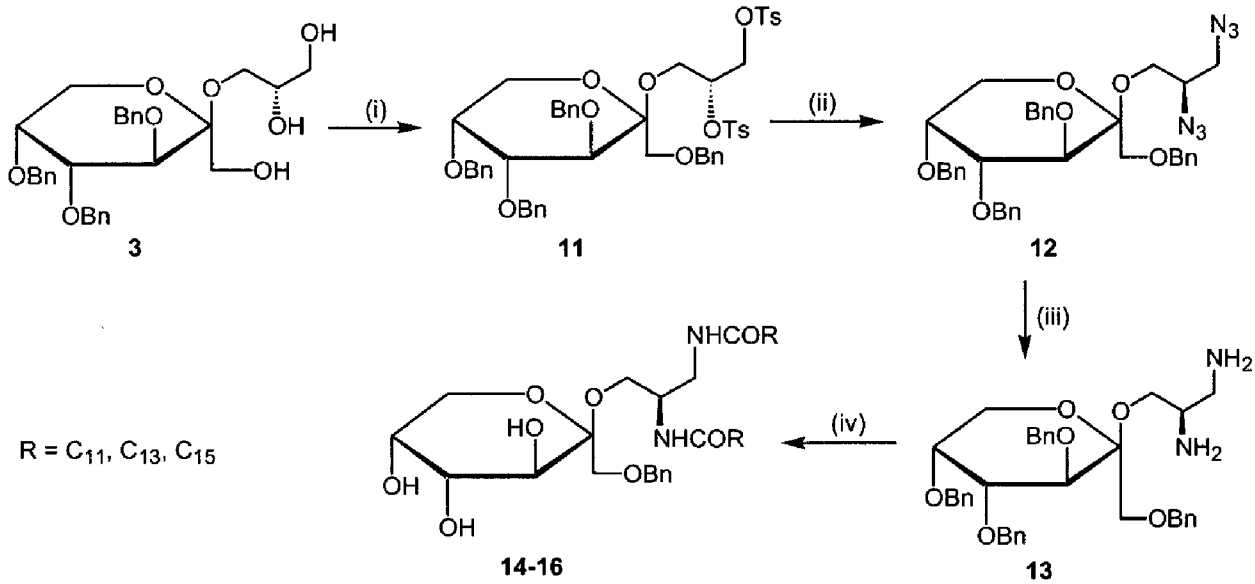


9 R_1 = OAc, R_2 = Ac



10 R_1 = OAc, R_2 = Ac

In **hoofdstuk 5** wordt de synthese behandeld van enkele lange-ketenderivaten van mono-acylamino- en bisacylaminoverbindingen uitgaande van diol **3**. De synthese van de bis-amide-derivaten **14-16** is weergegeven in Schema 1.



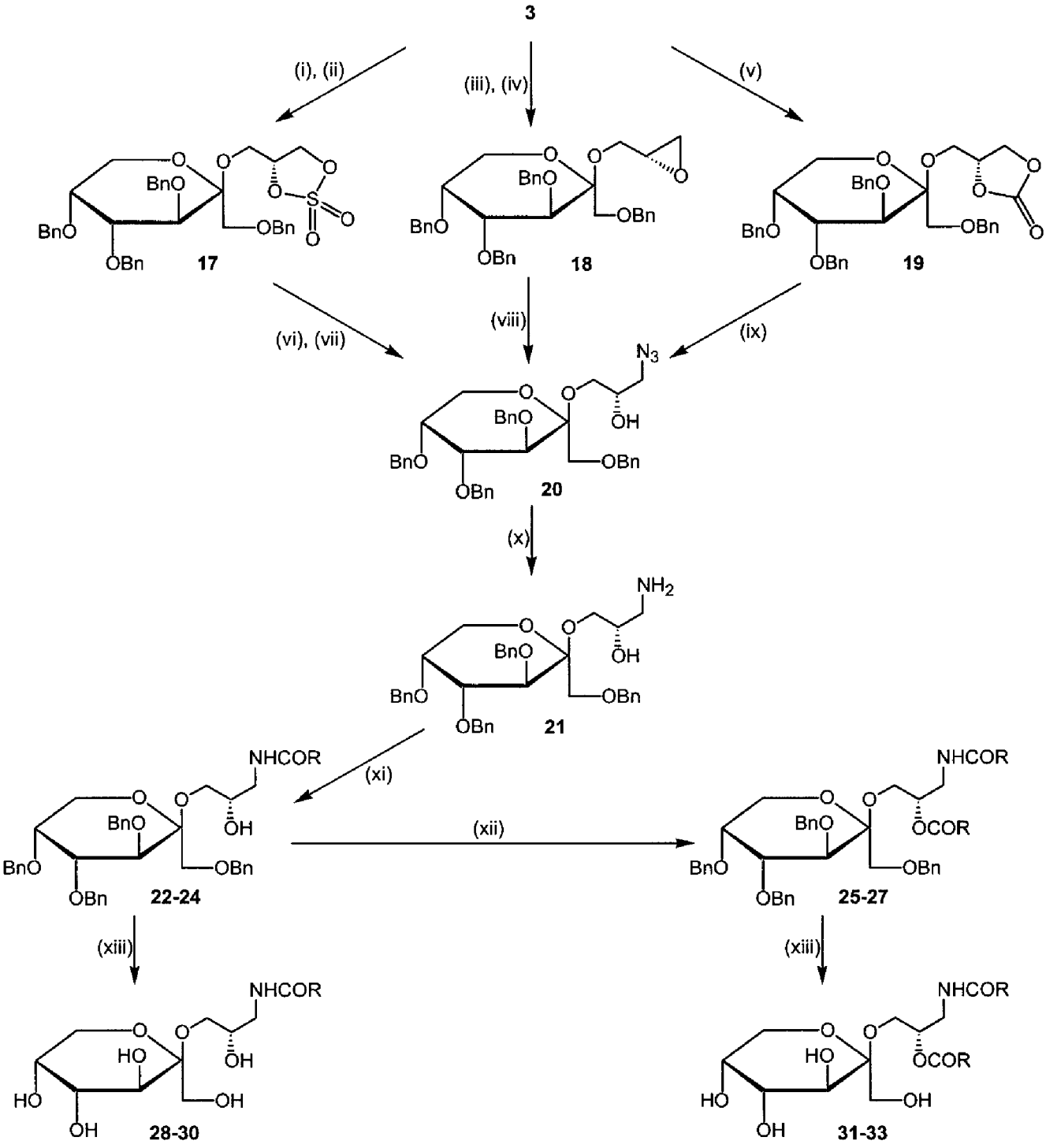
(i) pTsCl / pyridine
(ii) NaN_3 / DMF / 80 °C / 12 uur
(iii) $LiAlH_4$ / Et_2O
(iv) RCOCl / CH_2Cl_2 / Et_3N / 0 °C / 1 uur

Schema 1

Verbinding **20** is het belangrijke intermediair voor de synthese van mono-acylamino-derivaten. De verbinding kon worden verkregen via drie verschillende synthetische routes gebaseerd op een cyclisch sulfaat **17**, een oxiraan **18** of een cyclisch carbonaat **19** als tussenproduct (Schema 2).

Reductie van **20** gaf amino-alcohol **21**, waarna gecontroleerde acylering met vetzuurchloriden (lauroyl, myristoyl of palmitoyl) de corresponderende amiden **22-24** (64-72%) opleverde. Katalytische hydrogenering (H_2, Pd/C) van **22-24** resulteerde in de volledig ontschermde mono-amiden **28-30**. Acylering van de beschermde amiden **22-24** met dezelfde

zuurchloriden bij kamertemperatuur (25°C) gaf de overeenkomstige *O*-acylderivaten **25-27**. Op een analoge wijze resulteerde katalytische hydrogenering (H_2, Pd/C) in de gedebenzyleerde verbindingen **31-33** (Schema 2).

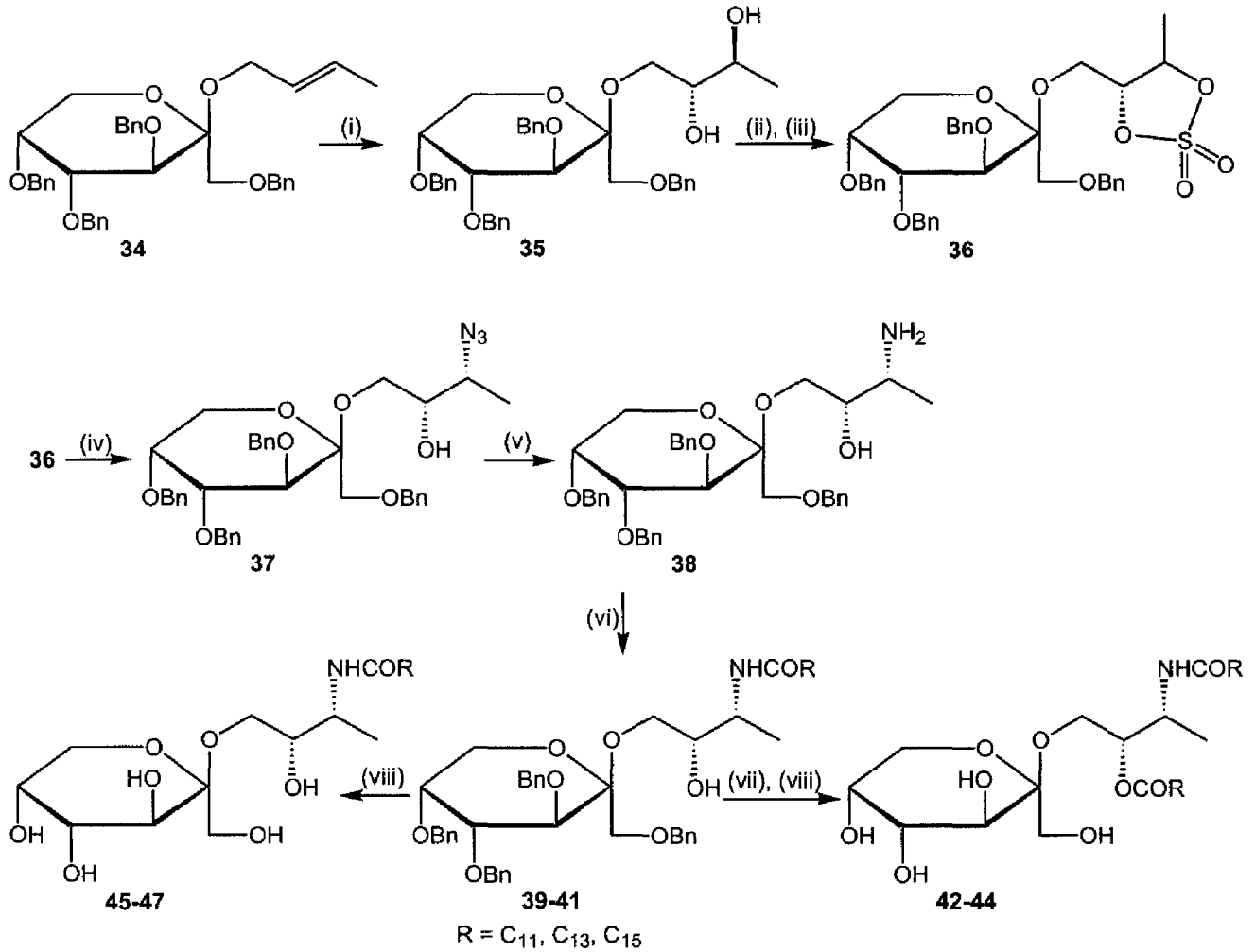


(i) pTsCl / pyridine
(ii) NaN_3 / DMF / 80 °C / 12 uur
(iii) $EtC(OEt)_3$ / Me_3SiCl / CH_2Cl_2 / 0 °C
(iv) K_2CO_3 / MeOH / kt of MeONa / CH_2Cl_2 / kt
(v) $(CH_3O)_2CO$ / DBU, 80 °C / 1 uur
(vi) LiN_3 / DMF / 80 °C / 1 uur
(vii) THF / geconc. H_2SO_4
(viii) NaN_3 / $(NH_4)_2SO_4$ / $CH_3OCH_2CH_2OH$ / H_2O / kt
(ix) NaN_3 / H_2O / DMF / 80-95 °C
(x) PPh_3 / pyridine / NH_3 opl.
(xi) RCOCl / CH_2Cl_2 / Et_3N / 0 °C / 1 uur
(xii) RCOCl / pyridine / DMAP / kt / 1 uur
(xii) H_2 -Pd(C) / MeOH / 2 uur

Schema 2

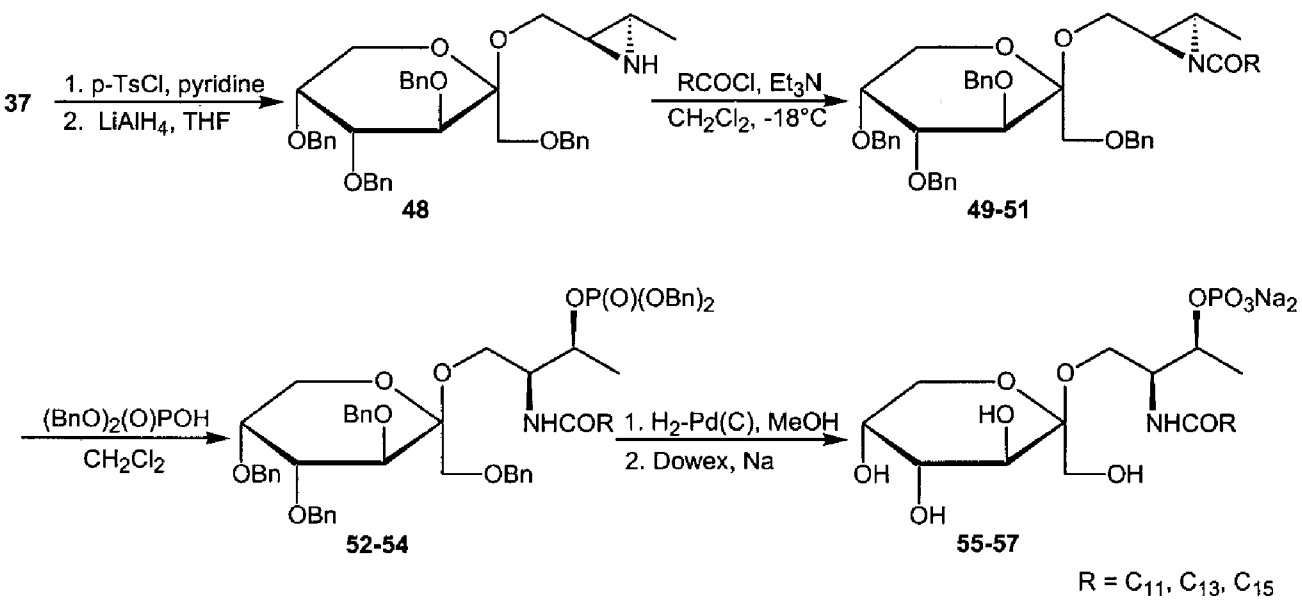
In **hoofdstuk 6** worden de synthese en reacties van but-2-enyl β-**D**-fructopyranoside beschreven. Stereoselectieve asymmetrische dihydroxylering volgens de Sharpless-methode van gebenzyleerd but-2-enyl β-**D**-fructopyranoside **34** leverde kristallijn **35** op. Het kon worden aangetoond, dat de absolute configuratie van de chirale centra in de aglyconeenheid van verbinding **35** 2(*R*),3(*R*) is. De omzetting van **35** in het azido-alkohol **37** werd gerealiseerd door middel van ringopening van het cyclische sulfaatderivaat **36**. Verbinding **37** werd vervolgens omgezet in amino-alkohol **38** door middel van een reductie met trifenylfosfine.

De synthese van acylaminoderivaten **39-41** uitgaande van het amino-alkohol **38** werd uitgevoerd met behulp van vetzuurchloriden (lauroyl, myristoyl en palmitoyl) als acylerend agens. De reactie van **39-41** met overmaat vetzuurchloride in aanwezigheid van katalytische hoeveelheden DMAP bij kamertemperatuur, gevolgd door katalytische hydrogenering (H_2, Pd/C) leverde verbindingen **42-44** op. Op identieke wijze werden de onbeschermde amidederivaten **45-47** verkregen door middel van katalytische hydrogenering van verbindingen **39-41** (Schema 3).



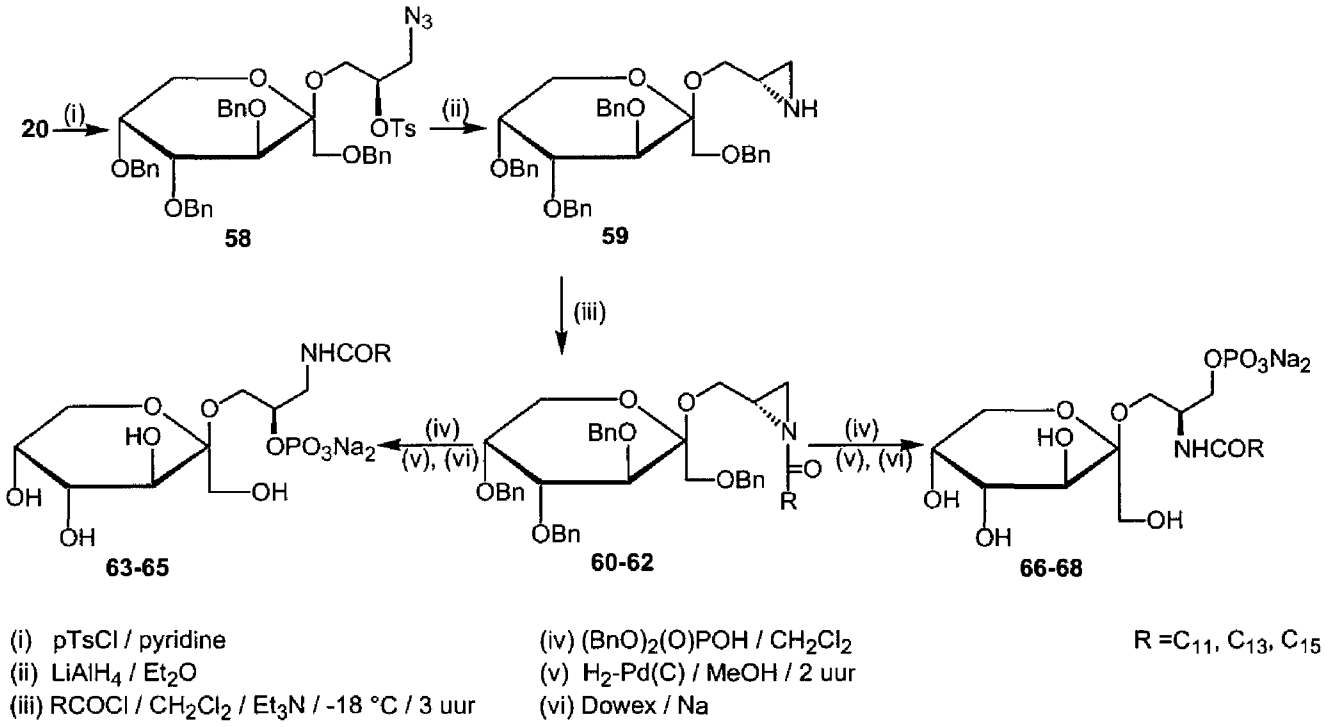
Schema 3

Omzetting van **37** in het overeenkomstige aziridinederivaat **48** (69%) werd op de gebruikelijke manier uitgevoerd. *N*-Acylaziridinederivaten **49-51** werden verkregen door de reactie van verbinding **48** met dezelfde vetzuurchloriden. Nucleofiele ringopening van deze geactiveerde derivaten met behulp van dibenzylwaterstoffosfaat bij kamertemperatuur leidde in alle gevallen tot de vorming van slechts één regio-isomeer. De aldus verkregen producten **52-54** werden onderworpen aan katalytische hydrogenering en werden vervolgens met behulp van een ionenwisselaar (Dowex-50W x2, natrium vorm) omgezet in de corresponderende dinatrium zouten **55-57** (Schema 4).



Schema 4

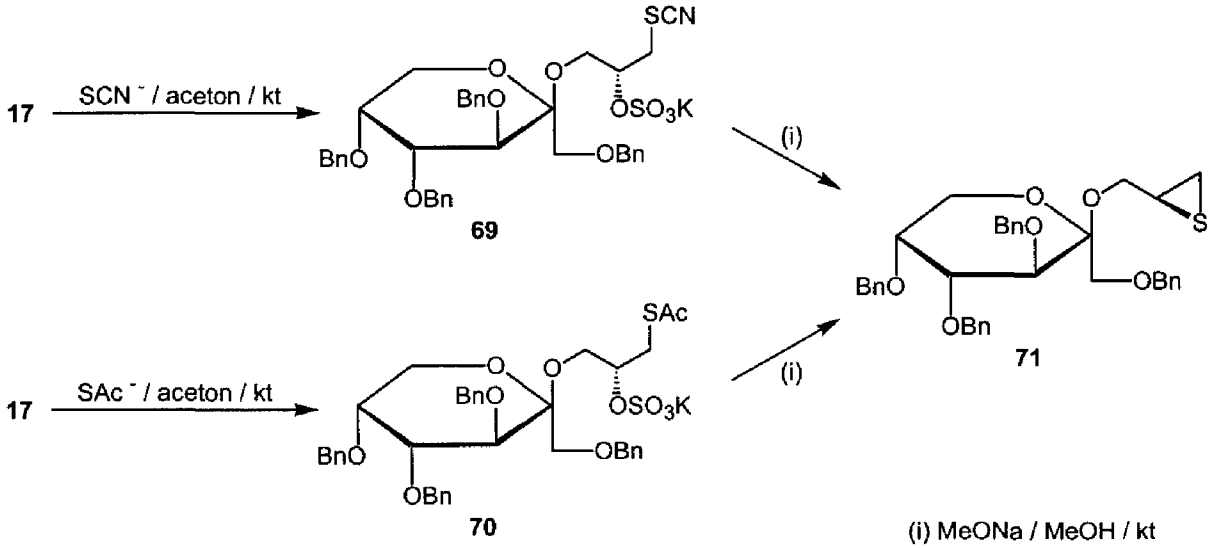
In **hoofdstuk 7** wordt de synthese van enkele acylaminofosfaten van 2,3-dihydroxyalkyl β-**D**-fructopyranosidederivaten beschreven. Een belangrijke intermediaire verbinding voor de synthese van deze derivaten is verbinding **59** die werd verkregen uit het azido-alkohol **20** door stapsgewijze behandeling met *p*-tolueensulfonylchloride in pyridine en lithiumaluminium-hydride. Pogingen om verbinding **59** te synthetiseren via een Staudinger-type reductie van het azido-alkohol **20** waren niet succesvol. Acylering van **59** met behulp van enkele vetzuur-chloriden resulteerde in de overeenkomstige *N*-acylaziridines **60-62** in redelijke opbrengsten. De bereiding van enkele acylaminofosfaten door middel van ringopening van de geactiveerde *N*-acylaziridines **60-62** met dibenzylwaterstoffosfaat werd onderzocht. In alle gevallen werd hier een mengsel van twee verbindingen verkregen. De zuivere regio-isomeren konden verkregen worden met behulp van kolomchromatografie. Wanneer deze reacties werden uitgevoerd bij -18°C gedurende *ca.* 3 uur, veranderde de productverhouding van 1:1 (bij 25°C) naar respectievelijk 4:1, 5:1 en 7:1. Met behulp van katalytische hydrogenering (H_2, Pd/C) werden de benzylgroepen verwijderd en vervolgens werden de producten omgezet in de zuivere dinatrium-zouten **63-68** (Schema 5) met behulp van een ionenwisselaar (Dowex-50W x2, natrium vorm).



(i) pTsCl / pyridine
(ii) $LiAlH_4$ / Et_2O
(iii) RCOCl / CH_2Cl_2 / Et_3N / -18 °C / 3 uur
(iv) $(BnO)_2(O)POH$ / CH_2Cl_2
(v) H_2-Pd(C) / MeOH / 2 uur
(vi) Dowex / Na
R = C_{11}, C_{13}, C_{15}

Schema 5

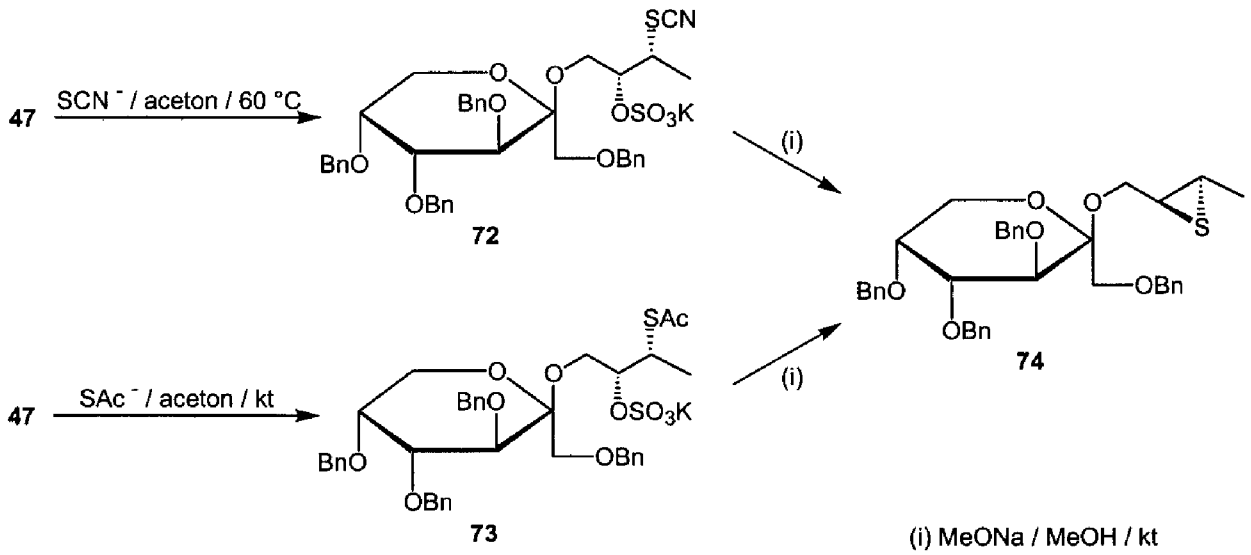
In **hoofdstuk 8** wordt de synthese behandeld van enkele epithioalkylglycosiden van **D**-fructose via twee conventionele routes. In de eerste methode werd episulfide **71** gesynthetiseerd uit verbinding **18** (zie hoofdstuk 5) door behandeling met kaliumthiocyanaat in waterige ethanol of 1,4-dioxaan (opbrengst 52-58%) of met thioureum in methanol (opbrengst 90%). De alternatieve methode gaat uit van het cyclische sulfaat **17** (zie hoofdstuk 5), dat met kaliumthiocyanaat wordt omgezet in het tussenproduct **69** (89%). Het episulfide **71** werd vervolgens in 51% opbrengst verkregen, wanneer **69** werd behandeld met een oplossing van natriummethoxide. De reactie van **17** met kaliumthioacetaat gaf het S-acetylderivaat **70**, dat daarna met behulp van natriummethoxide in methanol kon worden omgezet in verbinding **71** (Schema 6).



(i) MeONa / MeOH / kt

Schema 6

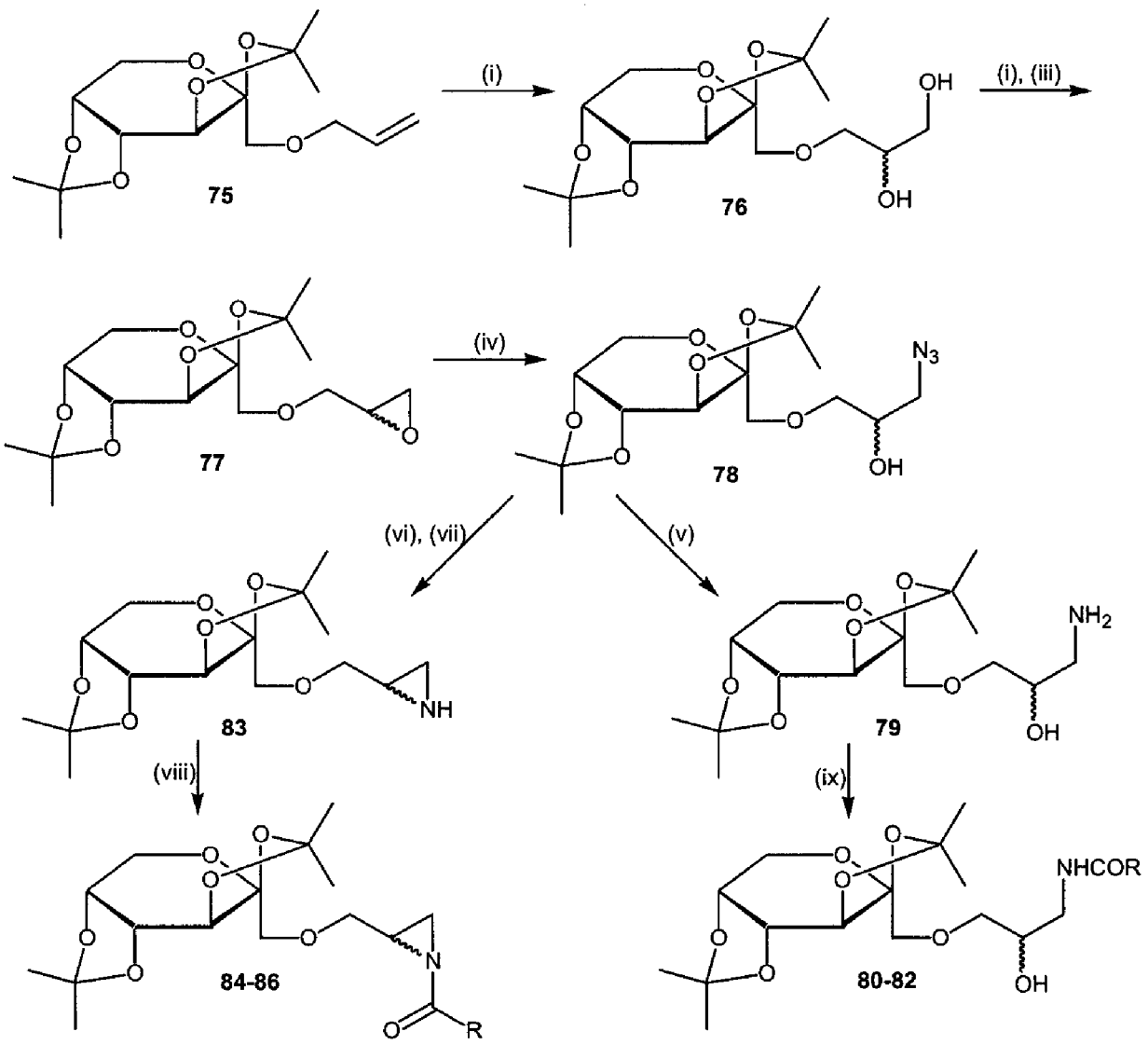
Verbinding **74** kon op een gelijke wijze worden verkregen uit het cyclische sulfaat **47** (zie hoofdstuk 6). Thiiraan **74** werd in hogere opbrengst verkregen (81%), wanneer het cyclische sulfaat **47** werd behandeld met kaliumthioacetaat in aceton, gevolgd door een reactie van het resulterende zout **73** met natriummethoxide in methanol (schema 7). Pogingen om de benzylether beschermgroepen van de episulfiden **71** en **74** te verwijderen waren niet succesvol, er werd slechts gedeeltelijke debenzylering waargenomen. Dit werd waarschijnlijk veroorzaakt door vergiftiging van de katalysator. Debenzylering met behulp van natrium in vloeibare ammoniak leidde eveneens tot slechte resultaten. Er werden complexe mengsels van producten gevormd, die niet gescheiden konden worden.



Schema 7

In **hoofdstuk 9** worden enkele voorlopige resultaten beschreven van de synthese van een 1-*O*-glycerylether en enkele daaraan gerelateerde verbindingen, uit 1-*O*-allyl-2,3:4,5-di-*O*-isopropylidene β-**D**-fructopyranose (**75**). Het sleutelproduct **76** in deze sequentie werd verkregen door eenvoudige dihydroxyleringsreacties van **75** met behulp van kaliumpermanganaat of kalium(VI)osmaat als oxiderende agentia. Verbinding **76** werd omgezet in het oxiraan **77** via standaard-procedures. Nucleofiele ringopening van het oxiraan **77** met natriumazide leverde azido-alkoholen **78** op als een diastereomeer mengsel dat vervolgens werd omgezet in de amino-alkoholen **79** en aziridinederivaten **83**. De verbindingen **79** werden verkregen wanneer verbindingen **78** werden gereduceerd met trifenylfosfine of lithiumaluminiumhydride. Omzetting van **78** in de aziridinederivaten **83** werd uitgevoerd via de monosulfonaatderivaten. Behandeling van de amino-alkoholen **79** en de aziridinederivaten **83** met vetzuurchloriden (lauroyl, myristoyl of palmitoyl) leverde de overeenkomstige mono-amidederivaten **80-82** en *N*-acylaziridines **84-86** op in redelijke opbrengsten. Er werden pogingen ondernomen om stereogecontroleerd derivaat **91** te verkrijgen door behandeling van verbinding **87** met (4*R*)-methaansulfonaatderivaat **88**. Reactie van **87** met het racemische monotosylaat **89** op dezelfde wijze als boven, gaf een onscheidbaar mengsel van ongereageerd **89** en verbinding **92**. Pogingen om verbinding **92** te verkrijgen door middel van reactie van **87** met verbinding **90** waren niet succesvol. De selectieve

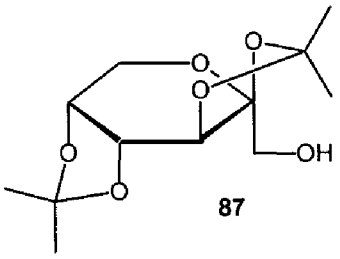
verwijdering van de exocyclische isopropylideengroepen van verbindingen **91** en **92** lukte evenmin.



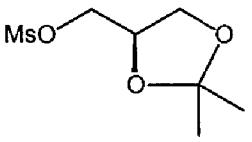
R = C_{11}, C_{13}, C_{15}

(i) AD-mix α/β of $KMnO_4$ / H_2O / aceton
(ii) $EtC(OEt)_3$ / Me_3SiCl / CH_2Cl_2 / 0 °C
(iii) K_2CO_3 / MeOH / kt of MeONa / CH_2Cl_2 / kt
(iv) NaN_3 / $(NH_4)_2SO_4$ / $CH_3OCH_2CH_2OH$ / H_2O / kt
(v) PPh_3 / pyridine / NH_3 opl. of $LiAlH_4$ / Et_2O
(vi) pTsCl / pyridine
(vii) $LiAlH_4$ / THF
(viii) RCOCl / CH_2Cl_2 / Et_3N / -18 °C / 1 uur
(ix) RCOCl / CH_2Cl_2 / Et_3N / 0 °C / 1 uur

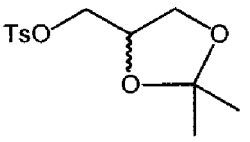
Schema 8



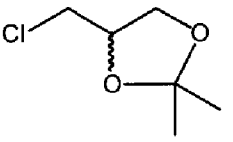
87



88



89



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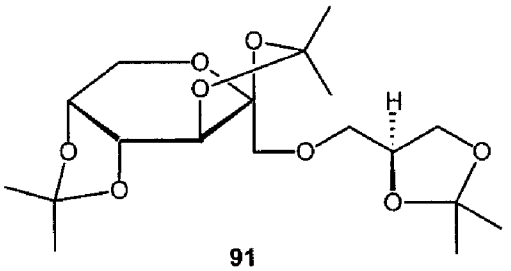
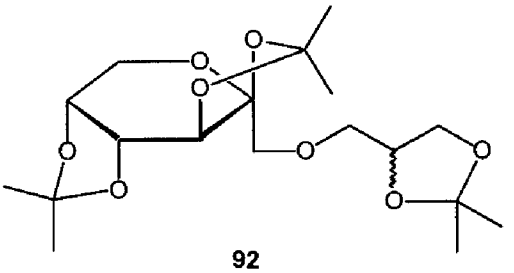


91



92

Al met al is het resultaat van het in deze dissertatie beschreven onderzoek, een veelheid aan nieuwe glyceroglycolipiden afgeleid van **D**-fructose.

PUBLICATIONS AND PRESENTATIONS

Synthesis and reactions of some derivatives of (3,6S,9R,10R,11S)-1,4,7-trioxaspiro[5,5] undecane-3,9,10,11-tetrol: Novel quasi-saccharides.

Regeling, H.; Sunghwa, F.; Zwanenburg, B.; de Gelder, R.; Chittenden, G.J.F. *Carbohyd. Polymers*, **1998**, *37*, 323.

Synthesis of some dihydroxyalkyl β-D-fructopyranosides - Fructosyl lipid derivatives.

Regeling, H.; Sunghwa, F.; Zwanenburg, B.; Chittenden, G.J.F. *In preparation.*

*Synthesis of oxiranyl-, aziridinyl- and epithio-alkylglycosides of **D**-fructose.*

Regeling, H.; Sunghwa, F.; Zwanenburg, B.; Chittenden, G.J.F. *In preparation*

*Synthesis and reactions of some glycerol derivatives of **D**-fructose.*

Sunghwa, F.; Schievers, S.; Regeling, H.; Zwanenburg, B.; Chittenden, G.J.F. *19th Internat. Carbohydrate Symp.*, Univ. of California, San Diego, California, Aug. 9-14, **1998**. (poster presentation)

CURRICULUM VITAE

Fortunatus Sung'hwa was born on 6 November 1963 in Kipalapala, in the Tabora region of western Tanzania. In 1972 he started his primary education at Kipalapala primary school and then he joined Uchama secondary school in Tabora for ordinary level education in 1979, which he completed successfully in 1982. In 1983, he undertook technical education at the Dar-es-Salaam Institute of Technology. Between 1991-1994 he studied for his Bachelor of Science (chemistry and applied microbiology) at the university of Dar-es-Salaam, which he obtained with honours. In 1994 he joined the group of Professor dr. Mayunga Nkunya at the University of Dar-es-Salaam to study for the degree of Master of Science. He specialized in phytochemistry studies on some medicinal plants of the family *Annoneceae*. In January 1997 he joined the University of Nijmegen, The Netherlands, for his Ph.D study in the group of Professor dr. Binne Zwanenburg and Dr. Gordon J.F. Chittenden. In January 2000 he returned to the University of Dar-es-Salaam where he is currently working in a research capacity.